Positive airway pressure therapy for post-stroke sleep disordered breathing: a systematic review, meta-analysis and meta-regression

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Shareable abstract (@ERSpublications)
Positive airway pressure therapy has been shown to reduce recurrent vascular events and have significant beneficial effects on neurological deficit, cognition, functional independence and daytime sleepiness in post-stroke patients with SDB. https://bit.ly/3gXgLNy

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Abstract

Background Sleep disordered breathing (SDB) is an under-recognised independent risk factor and a potential consequence of stroke. We systematically reviewed and meta-analysed the effectiveness of positive airway pressure (PAP) therapy in improving post-stroke outcomes.

Methods We searched CENTRAL, Embase, PubMed, CINAHL, PsycINFO, Scopus, ProQuest, Web of Science and CNKI (China National Knowledge Infrastructure) for randomised controlled trials comparing PAP therapy against a control or placebo group. We evaluated the pooled effects of PAP therapy on recurrent vascular events, neurological deficit, cognition, functional independence, daytime sleepiness and depression using random effects meta-analyses.

Results We identified 24 studies. Our meta-analyses showed that PAP therapy reduced recurrent vascular events (risk ratio 0.47, 95% CI 0.28–0.78), and showed significant beneficial effects on neurological deficit (Hedges' g= −0.79, 95% CI −1.19– −0.39), cognition (g=0.85, 95% CI 0.04–1.65), functional independence (g=0.45, 95% CI 0.01–0.88) and daytime sleepiness (g= −0.96, 95% CI −1.56– −0.37). However, there was insignificant reduction in depression (g= −0.56, 95% CI −2.15–1.02). No publication bias was detected.

Conclusions Post-stroke patients with SDB benefited from PAP therapy. Prospective trials are needed to determine the ideal initiation period and the minimum effective therapeutic dose.

Introduction

Sleep disordered breathing (SDB) is characterised by irregular respiratory patterns that result in poor ventilation during sleep [1]. It is both a risk factor and a consequence of stroke [2], with a post-stroke prevalence of up to 71% [3], and manifesting more commonly as obstructive sleep apnoea (OSA) [4]. Stroke-induced SDB could be caused by positional restriction, changes in airway muscle tone [5] or damage to the autonomic nervous control of the respiratory drive [6].

SDB causes frequent disruption to respiration during sleep, promoting cardiovascular instability through intermittent sympathetic nervous activation [7]. SDB also hinders neurological reconstruction crucial for patients' post-stroke recovery [8]. Previous studies have reported an increased risk of recurrent vascular

events [9] in post-stroke SDB patients; poorer outcomes in the domains of neurological deficit [10], which influences basic senses, reflex and consciousness [11]; cognition [12], referring to the higher-level function of the brain involved in the mental process of acquiring and comprehending information [13]; functional independence [14], referring to a person's ability to perform activities of daily living (ADL) [15]; daytime sleepiness [16]; and depression [17].

Positive airway pressure (PAP) therapy, the gold standard management for the general SDB population, works by stenting the airway open using air pressure, preventing interruption to the breathing pattern [18]. A current benchmark of 4 h of nightly PAP use was commonly applied to define acceptable therapy adherence [19]. However, poor adherence to therapy was widely reported [20]. To resolve this issue, device alterations to the PAP delivery route and/or mode were made to reduce discomfort [21]. Various device modifications have been made to improve comfort and adherence for PAP/continuous PAP (CPAP), including auto-titrating (auto-CPAP), bilevel PAP (bi-PAP), expiratory PAP (EPAP) and nasal routed PAP/CPAP [21]. The minimum effective dose of PAP therapy and the ideal device for the post-stroke SDB population has not been determined.

PAP therapy is a feasible treatment option due to the potential for safe and quick implementation [5]. However, its effectiveness for post-stroke SDB patients is not established due to inconsistent findings reported. For example, PAP therapy was observed to improve long-term cardiovascular survival [22], but not attributed to a significant reduction in risk of secondary stroke occurrence [23]. Additionally, PAP therapy was found to improve neurological recovery [23] and functional independence [24]. However, findings for other outcomes were inconsistent, with effectiveness [25] and ineffectiveness [24] found for cognition, and improvements [24] and insignificant changes [25, 26] found for daytime sleepiness.

Eight reviews on the use of PAP therapy for post-stroke SDB patients were identified, three including meta-analyses [27–29]. Of these three meta-analytic reviews, two included observational studies [28, 29]. A meta-analysis of purely randomised trials [27] found potential improvements for neurological deficit. Generally, reviews focusing on the feasibility of PAP therapy reported inconclusive findings [30–33], had substantial risks of bias [27, 30] and were likely underpowered [28–30, 34]. Due to the lack of studies and participants exploring other health outcomes, more adequately powered clinical trials were required. The existing reviews searched limited databases, which might have resulted in bias; we found that most included studies in these reviews were conducted in European countries and the USA, limiting their generalisability to the Asian population.

Due to the gaps in the existing reviews and inconclusive summary evidence on the effectiveness of PAP therapy in promoting recovery and ameliorating negative health outcomes in post-stroke SDB patients, diagnostic and treatment efforts may have been deterred. If proven effective, PAP could be confidently prescribed and administered as a safe and non-invasive treatment [5]. Therefore, we conducted a systematic review and pooled data meta-analysis of studies evaluating the effectiveness of PAP therapy in reducing recurrent vascular events (primary outcome) and improving other secondary health outcomes (neurological deficit, cognition, functional independence, daytime sleepiness and depression) in post-stroke patients with SDB compared with no treatment, usual care or placebo.

Methods

This review was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (supplementary table S1) [35]. The review protocol was registered at PROSPERO with identifier number CRD42020209226.

Information sources and search strategy

We systematically searched nine bibliographic databases (CENTRAL, Embase, PubMed, CINAHL, PsycINFO, Scopus, ProQuest, Web of Science and CNKI (China National Knowledge Infrastructure)), trial registries, grey literature and biomedical journals (supplementary table S2). A three-step search approach was formulated in collaboration with a senior librarian. In Step 1, a systematic search using combinations of MeSH (Medical Subject Headings) terms and key words was performed through the listed databases from inception to 19 August 2022. In Step 2, trial registries and repositories of results were searched for ongoing or unpublished studies to enhance the extensiveness of the search. Authors of unpublished and ongoing trials were contacted *via* e-mail for updates. Step 3 involved a search of grey literature sources, peer-reviewed biomedical journals and the references lists of included trials [36]. All key words and index terms were optimised to each database's search syntax. Supplementary table S3 presents the detailed search strategies for all bibliographic databases.

Eligibility criteria

The eligibility criteria were formulated based on the PICO (Population, Intervention, Comparators, Outcomes) elements [37] and the types of studies that may address the review question [38]. Randomised controlled trials (RCTs) should include: 1) post-stroke SDB patients that were aged ⩾18 years, 2) treatment with non-invasive PAP devices, 3) comparison against a control or placebo group, and 4) measurement of recurrent vascular events or post-stroke outcomes of neurological deficit, cognition, functional independence, daytime sleepiness and depression. The detailed eligibility criteria are defined in supplementary table S4.

Selection process

The PRISMA four-phase flow diagram was used to aid in the reporting and justification of the selection process [39]. Two reviewers (Z.A.T. and H.X.O.) independently performed the selection. Based on the eligibility criteria, titles and abstracts were first screened for relevance, then full-text articles were retrieved and reviewed. A third reviewer (H.G.H.) was consulted for disagreement until consensus was achieved.

Data extraction

Data extraction was conducted by two independent reviewers using a piloted and modified data extraction form. Items extracted included study characteristics (authors, year, country, study design, sampling procedures, sample size and attrition data), participants (age, type of stroke and SDB), interventions (type of PAP device, duration and co-interventions), comparators, outcomes (instruments, pre- and post-intervention scores, and timing of outcome measurements), data analysis (missing data management), key conclusions and funding sources. The corresponding author was contacted for any incomplete or missing data.

Risk of bias assessment

The same two reviewers independently undertook the risk of bias assessment using the Cochrane Collaboration's "RoB" risk of bias tool for randomised trials to evaluate the quality of evidence of individual studies based on bias arising from six domains [40]. The same third reviewer was involved in mediating discrepancies.

Data analyses and synthesis

Summary measures

Studies with continuous or dichotomous data on sleep outcomes were included in the meta-analysis using the metafor package in R software [41]. z-statistics with p-values of 0.05 were employed to evaluate the overall effect [42]. The summary statistics used for dichotomous and continuous data were risk ratio and Hedges' g, respectively, with 95% confidence intervals. Standardised mean difference was chosen for continuous data analyses due to the different instruments used for each outcome measure. The weighted average of the intervention's effect was calculated and the effect size was interpreted with Hedges' g. The effect size was reported as Hedges' g and was assessed as very small ($g \leqslant 0.01$), small ($g \geqslant 0.2$), medium ($g \geqslant 0.5$), large ($g \geqslant 0.8$), very large ($g \geqslant 1.2$) or huge ($g \geqslant 2.0$) [43]. In addition, the 95% prediction interval (95% PI) for the summary estimate with a random effects model was estimated to predict a range of true effects in a future similar study [44].

Methods of combined results

The Hartung–Knapp–Sidik–Jonkman (HKSJ) method was employed as the estimator for the random effects meta-analysis because it consistently produces lower error rates than the DerSimonian–Laird method, especially when the number of studies is small [45]. Risk ratio utilising the Mantel–Haenszel method was measured for dichotomous outcomes [42]. Findings were displayed through forest plots with the overall effect examined using z-tests [46].

Assessment of heterogeneity

Presence of heterogeneity of studies was determined through forest plot inspection and χ^2-statistics [47], and quantified through I^2-statistics, with $p<0.10$ in the Chi-squared test and $I^2>40\%$ indicating problems with heterogeneity [42]. Heterogeneity was investigated using sensitivity, subgroup analysis and meta-regression.

Sensitivity, subgroup and meta-regression analyses

Sensitivity analyses were performed by removing studies individually to identify sources of outstanding heterogeneity, followed by post-hoc investigation of identified studies [48]. Our team performed sensitivity analysis on trials conducted in the Chinese population because we noticed that these trials tended to report positive results. Subgroup analyses were performed through groups of prespecified effect modifiers

(including follow-up periods (⩽12 *versus* >12 months), therapy adherence levels (average duration of nightly use <4 *versus* ⩾4 h), phases of stroke (<2 *versus* ⩾2 weeks), type of PAP device used (auto-CPAP *versus* CPAP *versus* nasal CPAP) and baseline SDB severity (apnoea–hypopnoea index ⩽30 *versus* >30 events·h^{-1})) and analysing results across groups to determine the source of heterogeneity. A random effects meta-regression using the HKSJ model was conducted to explore the effect of covariates with the effect size of neurological deficit, functional independence and daytime sleepiness [49]. The meta-regression model included prespecified study-level covariates coded as continuous variables (mean age, proportion of male, sample size and year of publication). A p-value <0.05 indicates a significant moderator effect of the continuous variables [42].

Publication bias and overall quality of evidence

Funnel plots were used for assessing publication bias in outcomes with ⩾10 studies [50]. Further exploratory analyses using Egger's regression tests were performed for statistical assessment of asymmetry [51]. The confidence in the cumulative evidence of each outcome was evaluated by two independent reviewers (Z.A.T. and H.X.O.) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework and handbook [46].

Results

Summary of the search

The search process is summarised through a PRISMA flow diagram (figure 1). A total of 5140 records were generated from the nine bibliographic databases and other sources. Duplicates (n=1805) were

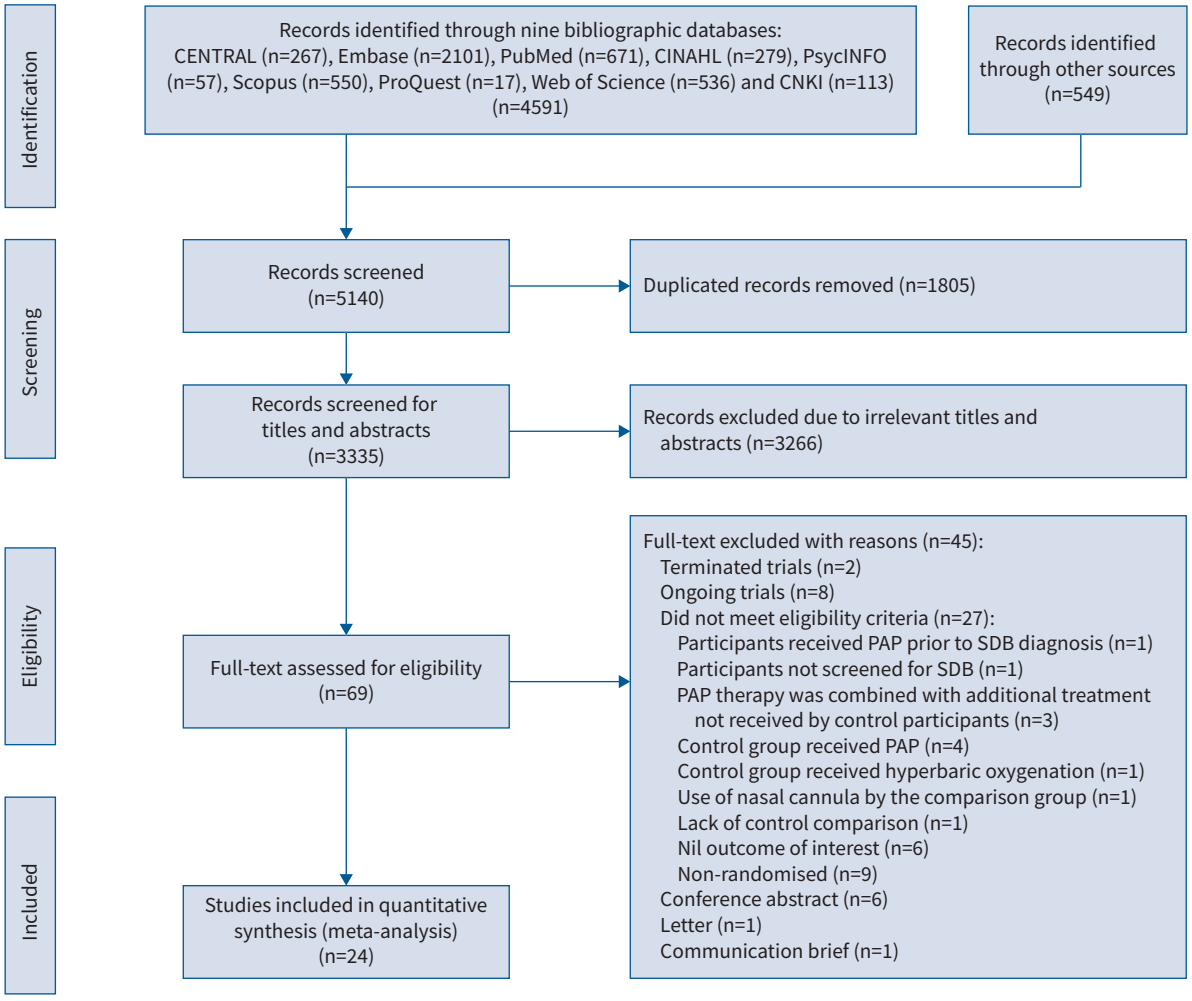

FIGURE 1 PRISMA-P flowchart for selection of studies included in the meta-analysis. PAP: positive airway pressure therapy; SDB: sleep disordered breathing.

removed, leaving 3335 records from which their titles and abstracts were further screened for exclusion through two independent reviewers. Screening of the titles and abstracts resulted in the exclusion of 3266 records, leaving 69 records that were downloaded for full-text assessment against the review's eligibility criteria. The full-text assessment resulted in the exclusion of 45 records, with the remaining 24 studies included for evidence synthesis. Characteristics of prominent but excluded studies are shown in supplementary table S5.

Summary of individual studies

The characteristics of the included studies are summarised in table 1 and supplementary table S6. The included studies primarily used the consecutive sampling method. The pooled sample included 1844 participants, ranging from 30 [26] to 145 [52] in each study. The κ-statistic between reviewers was 0.786, indicating substantial inter-rater agreement [53]. Attrition data were not reported in most Chinese studies and were high in three other studies [23, 54, 55]. Five authors were contacted *via* e-mail and/or ResearchGate messenger for the progress of ongoing trials (ClinicalTrials.gov: NCT01812993, NCT02554487 and NCT01561677) or full-text reports [56, 57], with one reply [57].

Risk of bias

Supplementary figure S1 summarises the risk of bias for each bias domain of all studies and provides a risk of bias summary for each included study. The explanations for the risk of bias judgement for each included study are reported in supplementary table S7.

The overall risk of bias was rated high in all trials, which was largely contributed to by the lack of participants or personnel blinding. Additionally, only eight (32%) of the included trials performed blinding of outcome assessors. 12 (48%) included studies were evaluated to be of unclear risk for the method of random sequence generation, 13 (52%) were judged to be high risk for incomplete outcome data and 19 (76%) were rated unclear for allocation concealment. One trial [23] was accorded high risk of selective reporting bias due to the reporting of non-prespecified outcomes. Finally, four (16%) studies were rated unclear for other bias due to possible sampling bias that may arise from the high rejection rate for study participation.

Effectiveness of PAP therapy on health outcomes

The scales used to measure each outcome are summarised in supplementary table S8.

Recurrent vascular events

Meta-analysis was performed on eight trials that measured recurrent vascular events among 678 patients (figure 2). The risk of recurrent vascular events in post-stroke SDB patients was 0.47 times lower (95% CI 0.28–0.78; $p<0.01$) in the PAP therapy compared with the control group, with no heterogeneity detected ($I^2=0\%$, $p=0.55$). The 95% PI values ranged from 0.14 to 1.58, suggesting that PAP therapy may not significantly lower the likelihood of recurrent vascular events relative to a comparator in future research with comparable conditions.

In addition, our sensitivity analysis showed that risk of recurrent vascular events in post-stroke SDB patients was 0.34 times lower (95% CI 0.17–0.70; $p<0.01$) in the PAP therapy compared with the control group after removal of three trials conducted in Chinese populations [52, 58, 59]. Parra and colleagues [22, 60] reported their data for recurrent vascular events twice in 2- and 5-year follow-ups. Only the 5-year follow-up data were used in the analysis to ensure a single representation of data from a population. No significant difference between subgroups was found (table 2 and supplementary figures S2–S6).

Secondary outcomes

Neurological deficit

12 trials that measured neurological deficit among 863 patients were included in the meta-analysis (figure 2). 10 trials used the National Institutes of Health Stroke Scale and two used the Canadian Neurological Scale. PAP therapy may result in a reduction in neurological deficit in post-stroke SDB patients when compared with control ($g=-0.79$, 95% CI −1.19– −0.39; $p<0.01$), with considerable heterogeneity ($I^2=86\%$, $p<0.01$). The 95% PI values ranged from −2.29 to 0.71, indicating that PAP therapy may not significantly reduce neurological deficit compared with a comparator in future studies with similar settings.

However, after removal of six trials conducted in Chinese populations [59, 61–65], our sensitivity analysis revealed that the effect size was reduced ($g=-0.22$, 95% CI −0.53–0.09; $p=0.16$) and the statistical heterogeneity was reduced ($I^2=37\%$, $p=0.16$). Subgroup analyses (supplementary figures S7–S11) show statistically significant reductions in neurological deficits for those who underwent PAP therapy for ⩽3 months

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TABLE 1 Characteristics of the included studies (n=24)

First author [ref.]	Year	Country	Total and group sample size (n); age (years)#	Stroke phase	Stroke type; SDB type	Attrition rate (n/N (%))	Missing data management	Funding; protocol registration
Aaronson [25]	2016	The Netherlands	T: 36 I: 20; 61.1±8.2 C: 16; 56.7±8.8	16.8 days after stroke	Ischaemic and haemorrhagic; OSA	I: 3/20 (15) C: 2/16 (12.5) T: 5/36 (13.9)	ITT analysis	No; yes
Bernasconi [88]	2020	Switzerland, Germany, Italy	T: 41 I: 19; 64.1±6.7 C: 22; 64.7±6.6	3 months after stroke	Ischaemic; CSA and OSA	I: 3/19 (15.8) C: 4/22 (18.2) T: 7/41 (17.1)	ITT analysis	Yes; yes
Bravata [23]	2011	USA	T: 55 I: 31; 70.6±9.4 C: 24; 71.6±13.3	⩽72 h of stroke	Ischaemic; CSA and OSA	I: 9/31 (29) C: 3/24 (12.5) T: 12/55 (21.8)	ITT analysis	Yes; yes
Bravata [54]	2010	USA	T: 70 I: 31; 66.3±11.9 C: 24; 67.4±12.8	Majority ⩽48 h of stroke	TIA; CSA and OSA	I: 9/45 (20) C: 5/25 (20) T: 14/70 (20)	ITT analysis	Yes; yes
Brown [55]	2013	USA	T: 32 I: 15; 61±22.22 C: 17; 70±19.3	⩽7 days of stroke	Ischaemic; CSA and OSA	I: 7/15 (46.7) C: 6/17 (35.3) T: 13/32 (40.6)	Unreported	Yes; yes
Cui [52]	2017	China	T: 145 I: 73; 66.2±5.6 C: 72; 68.4±13.9	Unspecified	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Dong [61]	2017	China	T: 80; 38–74	Unspecified; acute phase	Ischaemic; OSA	Unreported	Per-protocol analysis	Yes; no
Gao [62]	2013	China	T: 78 I: 44; 67.93±7.28 C: 34; 67.68±6.54	Unspecified; acute phase	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Gupta [89]	2018	India	T: 70 I: 30; 24±80 C: 40; 33±82.5	⩾6 weeks after stroke	Ischaemic and haemorrhagic; OSA	I: 4/34 (11.8) C: 0	Crossed over from I to C	Yes; yes
Hsu [26]	2006	UK	T: 30 I: 15; 76±5.93 C: 15; 71.67±8.89	Days 21–25 after stroke	No restriction; unclear	I: 5/15 33.3 C: 0 T: 5/30 (16.7)	ITT analysis	Yes; no
Kim [73]	2019	South Korea	T: 43 I: 20; 63.3±13.1 C: 20; 66.9±12.3	4.6±2.8 days after stroke onset	Ischaemic and haemorrhagic; CSA, OSA and mixed apnoea	I: 3/23 (13) C: 0 T: 3/43 (7)	Withdrawn patients excluded	Yes; yes
Li [63]	2020	China	T: 82 I: 39; 59.95±4.17 C: 43; 60.21±5.97	Unspecified	Ischaemic; OSA	Unreported	Per-protocol analysis	Unreported; no
Liu [58]	2014	China	T: 71 I: 34; 62.05±8.30 C: 37; 61.89±8.09	Unspecified	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Ning [66]	2019	China	T: 80 I: 37; 69.37±5.67 C: 43; 68.37±5.15	Unspecified; non-acute stroke	Ischaemic; OSA	Unreported	Unreported	Unreported; no

Continued

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TABLE 1 Continued

First author [ref.]	Year	Country	Total and group sample size (n); age (years)[#]	Stroke phase	Stroke type; SDB type	Attrition rate (n/N (%))	Missing data management	Funding; protocol registration
Parra [22]	2015	Spain	T: 140 I: 57; 63.7±9.1 C: 69; 65.5±9.1	4.6±2.8 days after stroke onset	Ischaemic; CSA and OSA	I: 14/71 (19.7) C: 0 T: 14/140 (10)	Per-protocol analysis	Yes; yes
Parra [60]	2011	Spain	T: 140 I: 57; 63.7±9.1 C: 69; 65.5±9.1	4.6±2.8 days after stroke onset	Ischaemic; CSA and OSA	I: 14/71 (19.7) C: 0 T: 14/140 (10)	Per-protocol analysis	Yes; yes
Ryan [24]	2011	Canada	T: 48 I: 22; 62.8±12.8 C: 22; 60.7±10.3	Within 3 weeks of stroke onset	Ischaemic and haemorrhagic; OSA	I: 3/25 (12) C: 1/23 (4.3) T: 4/48 (8.3)	Withdrawn patients excluded	Yes; yes
Sandberg [90]	2001	Sweden	T: 63 I: 31; 78.1±6.4 C: 28; 76.8±7.9	2–4 weeks after stroke	Ischaemic and haemorrhagic; CSA and OSA	I: 2/33 (6.1) C: 2/30 (6.7) T: 4/63 (6.3)	Missing data were replaced with mean	Yes; no
Su [68]	2011	China	T: 60 I: 30; 56–76 C: 30; 58–73	Unspecified; acute phase	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Tu [64]	2015	China	T: 140 I: 70; 48.15±9.85 C: 70; 47.68±8.96	Within 1 week of stroke	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Wan [67]	2018	China	T: 49 I: 20; 63.32±11.79 C: 29; 57.48±10.40	Unspecified; during hospitalisation	Unspecified; OSA	I: 5/25 (20) C: 0/29 T: 5/54 (9.3)	Withdrawn patients excluded	Yes; no
Wang [91]	2015	China	T: 86 I: 43; 64.5±9.7 C: 43; 64.2±8.6	Unspecified; acute phase	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Xu [65]	2020	China	T: 81 I: 41; 68.2±11.8 C: 40; 69.1±12.3	Unspecified; non-acute stroke	Ischaemic; OSA	Unreported	Unreported	Unreported; no
Yuan [59]	2016	China	T: 107 I: 51; 65.2±14.6 C: 56; 64.4±13.9	Unspecified	Unspecified; OSA	Unreported	Unreported	Unreported; no

[#]: Age data are presented as mean±SD or range. SDB: sleep disordered breathing; T: total; I: intervention; C: control; OSA: obstructive sleep apnoea; ITT: intention-to-treat; CSA: central sleep apnoea; TIA: transient ischaemic attack.

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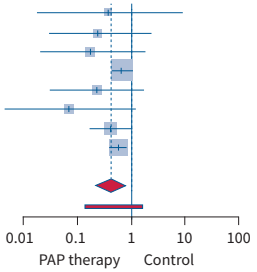
a)

First author [ref.]	PAP therapy Events	PAP therapy Total	Control Events	Control Total	Risk ratio (95% CI)	Weight (%)
Bernasconi [88]	0	16	1	18	0.37 (0.02–8.56)	2.5
Bravata [54]	1	31	3	24	0.26 (0.03–2.33)	4.7
Bravata [23]	1	45	3	25	0.19 (0.02–1.69)	4.6
Ciu [52]	25	73	35	72	0.70 (0.47–1.05)	30.5
Gupta [89]	1	30	6	40	0.22 (0.03–1.75)	5.2
Liu [58]	0	34	7	37	0.07 (0.00–1.22)	3.0
Parra [22]	6	57	17	69	0.43 (0.18–1.01)	18.1
Yuan [59]	21	51	40	56	0.58 (0.40–0.83)	31.4
Random effects model		337		341	0.47 (0.28–0.78)	100.0
95% prediction interval					(0.14–1.58)	

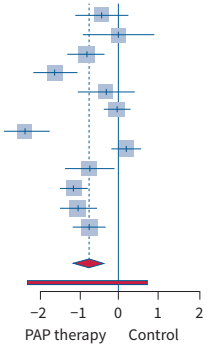
Heterogeneity: I^2=0%, τ^2=0.1800, p=0.55
Test for overall effect: z=−2.91, p<0.01



b)

First author [ref.]	PAP therapy Total	PAP therapy Mean±SD	Control Total	Control Mean±SD	SMD (95% CI)	Weight (%)
Aaronson [25]	20	−3.5±3.3	16	−2.2±2.7	−0.42 (−1.09–0.24)	7.8
Brown [55]	8	1.7±3.0	11	1.7±2.2	0.00 (−0.91–0.91)	6.5
Dong [61]	40	4.1±1.1	40	5.3±1.7	−0.82 (−1.27–−0.36)	8.8
Gao [62]	44	9.0±2.2	34	13.3±3.2	−1.60 (−2.11–−1.08)	8.5
Hsu [26]	15	2.3±2.2	15	3.3±3.7	−0.32 (−1.04–0.40)	7.5
Kim [73]	20	−1.5±1.3	20	−1.1±1.5	−0.28 (−0.90–0.34)	8.0
Li [58]	39	12.2±2.3	43	18.1±2.7	−2.34 (−2.91–−1.77)	8.3
Parra [60]	57	2.2±1.3	69	2.0±1.0	0.17 (−0.18–0.53)	9.3
Ryan [24]	22	1.9±1.7	22	3.1±1.5	−0.74 (−1.35–−0.12)	8.1
Tu [64]	70	14.4±3.2	70	18.0±3.2	−1.12 (−1.48–−0.77)	9.2
Xu [65]	41	13.2±3.8	40	17.5±4.5	−1.02 (−1.49–−0.56)	8.8
Yuan [59]	51	6.4±2.1	56	8.3±2.7	−0.78 (−1.17–−0.38)	9.1
Random effects model	427		436		−0.79 (−1.19–−0.39)	100.0
95% prediction interval					(−2.29–0.71)	

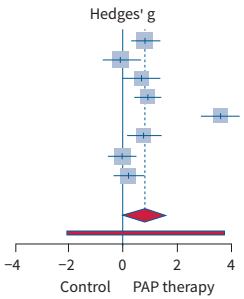
Heterogeneity: I^2=86%, τ^2=0.4115, p<0.01
Test for overall effect: z=−3.89, p<0.01



c)

First author [ref.]	PAP therapy Total	PAP therapy Mean±SD	Control Total	Control Mean±SD	SMD (95% CI)	Weight (%)
Gupta [89]	30	28.7±1.5	40	26.8±2.5	0.85 (0.36–1.35)	12.8
Hsu [26]	15	27.7±3.0	15	28.0±3.7	−0.10 (−0.81–0.62)	12.1
Kim [73]	20	4.0±3.4	20	2.2±1.9	0.64 (0.00–1.28)	12.4
Li [63]	39	25.6±3.0	43	22.3±4.0	0.92 (0.46–1.38)	12.9
Ning [66]	37	25.1±1.6	43	20.5±0.8	3.61 (2.89–4.33)	12.1
Ryan [24]	22	4.8±0.3	22	4.6±0.2	0.77 (0.16–1.38)	12.4
Sandberg [90]	31	2.6±4.0	28	2.8±4.1	−0.05 (−0.56–0.46)	12.7
Wan [67]	20	23.4±4.8	29	22.4±4.7	0.20 (−0.37–0.77)	12.6
Random effects model	214		240		0.85 (0.04–1.65)	100.0
95% prediction interval					(−2.09–3.78)	

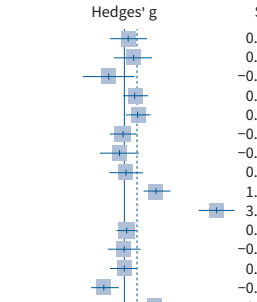
Heterogeneity: I^2=91%, τ^2=1.2669, p<0.01
Test for overall effect: z=2.05, p=0.04



d)

First author [ref.]	PAP therapy Total	PAP therapy Mean±SD	Control Total	Control Mean±SD	SMD (95% CI)	Weight (%)
Aaronson [25]	20	1.2±0.8	16	1.0±0.9	0.16 (−0.50–0.82)	5.7
Bernasconi [88]	17	99.0±2.8	16	94.2±20.2	0.33 (−0.36–1.02)	5.6
Brown [55]	8	95.0±7.4	11	98.3±3.7	−0.57 (−1.51–0.36)	5.0
Dong [61]	40	85.3±43.2	40	72.2±14.3	0.40 (−0.04–0.85)	6.1
Gao [62]	44	50.8±10.6	34	45.5±9.8	0.51 (0.06–0.97)	6.1
Gupta [89]	30	95.3±16.9	40	96.6±20.0	−0.06 (−0.54–0.41)	6.1
Hsu [26]	15	16.7±6.7	15	17.7±2.2	−0.20 (−0.91–0.52)	5.5
Kim [73]	20	14.0±9.8	20	13.5±9.9	0.05 (−0.57–0.67)	5.8
Li [63]	39	59.2±5.6	43	50.4±9.0	1.15 (0.68–1.62)	6.1
Ning [66]	37	70.5±2.8	43	62.5±1.9	3.36 (2.67–4.05)	5.6
Parra [60]	57	94.3±10.9	69	93.1±15.8	0.09 (−0.26–0.44)	6.3
Ryan [24]	22	105.6±16.8	22	105.8±13.9	−0.01 (−0.60–0.58)	5.8
Sandberg [90]	31	1.1±4.1	28	1.1±3.6	0.00 (−0.51–0.51)	6.0
Su [68]	30	90.8±15.3	30	99.0±4.5	−0.72 (−1.24–−0.19)	6.0
Wan [67]	43	96.3±3.5	43	87.8±10.3	1.10 (0.64–1.55)	6.1
Xu [65]	41	57.2±11.5	40	47.4±8.7	0.95 (0.49–1.41)	6.1
Yuan [59]	51	67.2±14.3	56	53.6±13.1	0.99 (0.58–1.39)	6.2
Random effects model	545		566		0.45 (0.01–0.88)	100.0
95% prediction interval					(−1.47–2.36)	

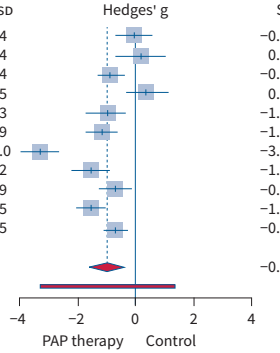
Heterogeneity: I^2=88%, τ^2=0.7569, p<0.01
Test for overall effect: z=2.02, p=0.04



e)

First author [ref.]	PAP therapy Total	PAP therapy Mean±SD	Control Total	Control Mean±SD	SMD (95% CI)	Weight (%)
Aaronson [25]	20	0.0±1.4	16	0.1±1.4	−0.06 (−0.71–0.60)	9.0
Brown [55]	8	7.7±2.2	11	7.0±4.4	0.17 (−0.74–1.09)	8.2
Gupta [89]	30	3.0±1.2	40	6.1±4.4	−0.90 (−1.40–−0.41)	9.4
Hsu [26]	15	2.7±2.2	15	2.0±1.5	0.35 (−0.38–1.07)	8.8
Kim [73]	20	−2.3±2.3	20	0.6±3.3	−1.00 (−1.66–−0.34	9.0
Liu [58]	34	3.0±2.5	37	7.0±3.9	−1.21 (−1.72–−0.71)	9.4
Ning [66]	37	60.3±1.3	43	68.3±3.0	−3.33 (−4.01–−2.64)	8.9
Ryan [24]	22	1.8±1.0	22	4.5±2.2	−1.55 (−2.23–−0.87)	8.9
Wan [67]	20	4.5±3.9	29	8.8±6.9	−0.71 (−1.30–−0.12)	9.2
Xu [65]	41	6.1±1.8	40	9.5±2.5	−1.55 (−2.05–−1.05)	9.4
Yuan [59]	51	4.7±2.4	56	6.1±1.5	−0.70 (−1.09–−0.31)	9.7
Random effects model	298		329		−0.96 (−1.56–−0.37)	100.0
95% prediction interval					(−3.22–1.29)	

Heterogeneity: I^2=88%, τ^2=0.9029, p<0.01
Test for overall effect: z=−3.19, p=0.01



f)

First author [ref.]	PAP therapy Total	PAP therapy Mean±SD	Control Total	Control Mean±SD	SMD (95% CI)	Weight (%)
Aaronson [25]	20	0.4±3.0	16	0.1±4.2	0.09 (−0.57–0.75)	14.4
Brown [55]	8	5.0±1.5	11	2.3±0.7	2.30 (1.08–3.53)	13.6
Hsu [26]	15	6.0±3.7	15	4.0±1.5	0.69 (−0.05–1.43)	14.3
Ning [66]	37	7.6±0.6	43	12.0±1.2	−4.74 (−5.62–−3.87)	14.2
Ryan [24]	22	4.3±5.7	22	6.2±7.0	−0.29 (−0.89–0.30)	14.5
Sandberg [90]	31	−5.4±11.7	28	1.8±8.5	−0.69 (−1.21–−0.16)	14.6
Wan [67]	20	0.7±1.5	29	5.7±5.2	−1.20 (−1.82–−0.57)	14.5
Random effects model	153		164		−0.56 (−2.15–1.02)	100.0
95% prediction interval					(−6.36–5.23)	

Heterogeneity: I^2=95%, τ^2=4.4286, p<0.01
Test for overall effect: z=−0.69, p=0.49

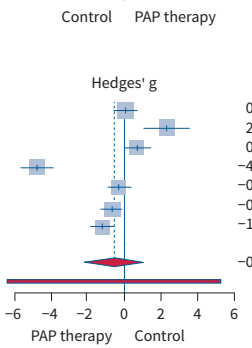


FIGURE 2 Forest plot of risk ratio or Hedges' g (95% CI) showing the effectiveness of positive airway pressure therapy (PAP) on a) recurrent vascular events, b) neurological deficit, c) cognition, d) functional independence, e) daytime sleepiness and f) depression. SMD: standardised mean difference.

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TABLE 2 Subgroup analyses of primary and secondary outcomes (n=24 studies)

Outcome and subgroups	Studies (n)	Total (n)	Risk ratio[#] or Hedges' g[¶]	95% CI	95% PI	Heterogeneity I^2 (%), τ^2, p-value	z-test, p-value[+]	Subgroup difference (χ^2), p-value[+]
Recurrent vascular events (n=8)								
Follow-up period								
⩽12 months	6	518	0.45	0.23–0.87	0.08–2.57	7, 0.28, 0.37	−2.37, **0.02**	0.01, 0.92
>12 months	2	160	0.42	0.18–0.97		0, <0.01, 0.94	−2.03, **0.04**	
Adherence								
<4 h								NA
⩾4 h	8	678	0.47	0.28–0.78	0.14–1.58	0, 0.18, 0.55	−2.91, **<0.01**	
Stroke phase								
<2 weeks	3	251	0.36	0.16–0.80	0.00–97.19	0, 0.03, 0.75	−2.51, **0.01**	0.42, 0.81
⩾2 weeks	2	104	0.26	0.05–1.46		0, 0.005, 0.79	−1.53, 0.13	
PAP device								
Auto-CPAP	7	552	0.46	0.25–0.85	0.11–1.96	0, 0.22, 0.49	−2.51, **0.01**	0.02, 0.88
CPAP								
Nasal CPAP	1	126	0.43	0.18–1.01				
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	5	448	0.46	0.22–0.98	0.05–4.37	11, 0.35, 0.35	−2.02, **0.04**	0.10, 0.75
AHI >30 events·h^{-1}	3	230	0.39	0.17–0.85	0.00–77.20	0, 0.01, 0.85	−2.37, **0.02**	
Neurological deficit (n=12)								
Follow-up period								
⩽3 months	11	756	−0.73	−1.05– −0.41	−1.85–0.39	78, 0.22, <0.01	−4.43, **<0.01**	1.19, 0.55
3–6 months	2	162	−1.32	−3.28–0.64		97, 1.92, <0.01	−1.32, 0.19	
>6 months	2	233	−0.30	−1.20–0.61		92, 0.39, <0.01	−0.64, 0.52	
Adherence								
<4 h	3	85	−0.29	−0.73–0.15	−3.36–2.78	0, 0.01, 0.76	−1.28, 0.20	8.45, **0.01**
⩾4 h	8	638	−0.92	−1.45– −0.38	−2.81–0.98	90, 0.53, <0.01	−3.37, **<0.01**	
Stroke phase								
<2 weeks	4	325	−0.34	−0.93–0.25	−2.96–2.28	89, 0.28, <0.01	−1.13, 0.26	4.72, 0.09
⩾2 weeks	4	191	−0.68	−1.05– −0.31	−1.93–0.56	17, 0.05, 0.31	−3.63, **<0.01**	
PAP device								
Auto-CPAP	5	425	−0.97	−1.45– −0.49	−2.66–0.73	65, 0.22, 0.02	−3.98, **<0.01**	10.83, **0.01**
CPAP	4	242	−1.08	−1.92– −0.25	−4.97–2.80	88, 0.63, <0.01	−2.55, **0.01**	
Nasal CPAP	2	156	0.02	−0.45–0.49		31, 0.05, 0.23	0.09, 0.93	
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	6	470	−1.13	−1.75– −0.50	−3.32–1.07	84, 0.52, <0.01	−3.54, **<0.01**	8.22, **0.02**
AHI >30 events·h^{-1}	5	312	−0.31	−0.67–0.05	−1.42–0.80	66, 0.09, 0.02	−1.69, 0.09	

Continued

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TABLE 2 Continued

Outcome and subgroups	Studies (n)	Total (n)	Risk ratio[#] or Hedges' g[¶]	95% CI	95% PI	Heterogeneity I^2 (%), τ^2, p-value	z-test, p-value[+]	Subgroup difference (χ^2), p-value[+]
Cognition (n=8)								
Follow-up period								
⩽1 month	4	225	0.28	−0.16–0.73	−1.55–2.12	60, 0.13, 0.06	1.24, 0.22	2.79, 0.25
1–3 months	3	161	0.25	−0.12–0.62	−2.92–3.42	0, 0.03, 0.42	1.33, 0.18	
3–6 months	3	232	1.77	0.02–3.53	−20.7–24.2	96, 2.32, <0.01	1.98, 0.05	
Adherence								
<4 h	1	30	−0.10	−0.81–0.62				3.43, **0.06**
⩾4 h	7	424	0.98	0.10–1.86	−2.20–4.16	92, 1.33, <0.01	2.17, **0.03**	
Stroke phase								
<2 weeks	1	40	0.64	0.00–1.28				0.32, 0.85
⩾2 weeks	5	283	1.01	−0.30–2.32	−4.12–6.14	95, 2.15, <0.01	1.51, 0.13	
PAP device								
Auto-CPAP	2	119	0.54	−0.07–1.16		65, 0.13, 0.09	1.73, 0.08	7.18, 0.07
CPAP	3	206	1.75	−0.03–3.54	−21.0–24.5	95, 2.39, <0.01	1.93, 0.05	
Nasal CPAP	2	89	−0.06	−0.48–0.35		0, <0.01, 0.92	−0.30, 0.76	
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	2	126	0.87	0.50–1.23		0, <0.01, 0.70	4.60, **<0.01**	62.0, **<0.01**
AHI >30 events·h^{-1}	5	248	0.33	−0.06–0.72	−0.91–1.56	55, 0.11, 0.07	1.64, 0.10	
Functional independence (n=17)								
Follow-up period								
⩽3 months	13	765	0.29	−0.10–0.68	−1.21–1.79	85, 0.42, <0.01	1.46, 0.14	0.93, 0.63
3–6 months	5	342	0.93	−0.32–2.19	−3.96–5.83	95, 1.95, <0.01	1.46, 0.14	
>6 months	4	336	0.34	−0.13–0.81	−1.70–2.38	80, 0.17, <0.01	1.42, 0.16	
Adherence								
<4 h	3	85	−0.14	−0.64–0.36	−4.39–4.11	0, 0.05, 0.44	−0.56, 0.58	4.38, 0.11
⩾4 h	12	880	0.63	0.11–1.16	−1.45–2.72	89, 0.81, <0.01	2.35, **0.02**	
Stroke phase								
<2 weeks	3	185	−0.03	−0.44–0.38	−3.91–3.85	0, 0.05, <0.01	1.35, 0.18	3.68, 0.16
⩾2 weeks	8	433	0.56	−0.25–1.37	−2.39–3.51	92, 1.28, 0.00	1.52, 0.13	
PAP device								
Auto-CPAP	6	388	0.42	−0.05–0.89	−1.14–1.98	75, 0.26, <0.01	1.77, 0.08	3.85, 0.28
CPAP	6	382	0.71	−0.42–1.84	−3.44–4.87	95, 1.91, <0.01	1.24, 0.22	
Nasal CPAP	3	215	0.02	−0.26–0.30	−1.90–1.94	0, <0.01, 0.78	0.15, 0.88	
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	5	330	0.48	−0.12–1.08	−1.72–2.68	79, 0.38, <0.01	1.57, 0.12	2.83, 0.24
AHI >30 events·h^{-1}	8	474	0.11	−0.09–0.31	−0.26–0.47	0, 0.01, 0.83	1.05, 0.30	

Continued

https://doi.org/10.1183/16000617.0169-2022

TABLE 2 Continued

Outcome and subgroups	Studies (n)	Total (n)	Risk ratio[#] or Hedges' g[¶]	95% CI	95% PI	Heterogeneity I^2 (%), τ^2, p-value	z-test, p-value[+]	Subgroup difference (χ^2), p-value[+]
Daytime sleepiness (n=11)								
Follow-up period	9	440	−0.59	−1.06– −0.13	−2.20–1.01	80, 0.40, <0.01	−2.50, **0.01**	1.96, 0.38
⩽3 months	3	221	−1.57	−3.26–0.12	−23.2–20.1	96, 2.15, <0.01	−1.82, 0.07	
3–6 months	3	248	−0.91	−1.24– −0.58	−3.98–2.15	18, 0.03, 0.29	−5.42, **<0.01**	
Adherence								
<4 h	3	85	0.14	−0.30–0.58	−2.91–3.19	0, 0.01, 0.72	0.61, 0.54	21.4, **<0.01**
⩾4 h	7	471	−1.37	−2.05– −0.70	−3.76–1.01	88, 0.74, <0.01	4.45, **0.00**	
Stroke phase								
<2 weeks	2	59	−0.46	−1.56–0.64		76, 0.46, 0.04	−0.82, 0.41	0.86, 0.65
⩾2 weeks	6	341	−1.17	−2.21– −0.14	−4.95–2.60	93, 1.57, <0.01	−2.22, **0.03**	
PAP device								
Auto-CPAP	6	397	−0.88	−1.32– −0.43	−2.34–0.59	66, 0.23, 0.01	−3.86, **<0.01**	10.45, **0.02**
CPAP	3	160	−1.64	−3.48–0.19	−25.0–21.8	96, 2.51, <0.01	−1.75, 0.08	
Nasal CPAP	1	30	0.35	−0.38–1.07				
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	4	241	−0.87	−1.56– −0.17	−4.00–2.26	73, 0.40, 0.01	−2.44, **0.01**	4.79, 0.09
AHI >30 events·h^{-1}	5	225	−0.49	−1.00–0.02	−2.25–1.27	67, 0.24, 0.02	−1.88, **0.06**	
Depression (n=7)								
Follow-up period								
⩽1 month	3	139	−0.33	−0.79–0.14	−5.00–4.34	40, 0.08, 0.19	−1.38, 0.17	0.08, 0.78
>1 month	4	178	−0.75	−3.70–2.2	−15.1–13.6	97, 8.86, <0.01	−0.50, 0.62	
Adherence								
<4 h	3	85	0.94	−0.30–2.18	−14.1–15.9	80, 0.99, <0.01	1.49, 0.14	4.95, **0.03**
⩾4 h	4	232	−1.71	−3.69–0.27	−11.3–7.89	96, 3.96, <0.01	−1.69, 0.09	
Stroke phase								
<2 weeks	1	19	2.30	1.08–3.53				25.2, **<0.01**
⩾2 weeks	5	249	−0.98	−2.85–0.90	−8.35–6.39	96, 4.45, <0.01	−1.02, 0.31	
PAP device								
Auto-CPAP	2	68	0.51	−2.86–3.88		96, 5.67, <0.01	0.30, 0.77	1.11, 0.57
CPAP	3	160	−1.64	−4.65–1.38	−40.5–37.2	98, 6.98, <0.01	−1.06, 0.29	
Nasal CPAP	2	89	−0.03	−1.33–1.27		89, 0.78, <0.01	−0.04, 0.97	
Baseline SDB severity								
AHI ⩽30 events·h^{-1}	2	63	0.95	−1.53–3.42		93, 2.95, <0.01	0.75, 0.45	60.5, **<0.01**
AHI >30 events·h^{-1}	4	174	−0.30	−1.10–0.51	−3.98–3.39	83, 0.57, <0.01	−0.72, 0.47	

95% CI: 95% confidence interval; 95% PI: 95% prediction interval; (C)PAP: (continuous) positive airway pressure; SDB: sleep disordered breathing; AHI: apnoea–hypopnoea index; NA: not applicable. [#]: risk ratio was used to report recurrent vascular events only; [¶]: Hedges' g was used to report neurological deficit, cognition, functional independence and daytime sleepiness; [+]: bold indicates statistically significant.

(g= −0.73, 95% CI −1.05– −0.41), used PAP for ⩾4 h per night (g= −0.92, 95% CI −1.45– −0.38), initiated PAP ⩾2 weeks after stroke incident (g= −0.68, 95% CI −1.05– −0.31), used CPAP (g= −1.08, 95% CI −1.92– −0.25) and the auto-CPAP device (g= −0.97, 95% CI −1.45– −0.49), and had mild-to-moderate baseline SDB severity (g= −1.13, 95% CI −1.75– −0.50). Test for subgroup difference (table 2) was significant for therapy adherence levels (p=0.01), type of PAP device used (p=0.01) and baseline SDB severity (p=0.02). Meta-regression analyses demonstrated that covariates have no effect on neurological deficit (table 3).

Cognition

Eight trials that measured cognition among 454 patients were pooled in the meta-analysis (figure 2). Six trials used the Mini-Mental State Examination, one used the Montreal Cognitive Assessment and one used the cognitive subscale of the Canadian Neurological Scale. PAP therapy may result in an improvement in cognition in post-stroke SDB patients when compared with control (g=0.85, 95% CI 0.04–1.65; p=0.04), with considerable heterogeneity (I^2=91%, p<0.01). The 95% PI values ranged from −2.09 to 3.78, indicating that PAP therapy may not significantly improve cognition relative to a comparator in future studies conducted in comparable contexts.

Our sensitivity analysis revealed that the effect size of PAP therapy in improving cognition in post-stroke SDB patients was reduced (g=0.44, 95% CI 0.02–0.86; p=0.04) and statistical heterogeneity reduced (I^2=59%, p=0.04) after removal of three trials conducted in Chinese populations [63, 66, 67]. Subgroup analyses (supplementary figures S12–S16) showed statistically significant improvement in studies that used PAP for ⩾4 h per night (g=0.98, 95% CI 0.10–1.86) and in those with mild-to-moderate baseline SDB severity (g=0.87, 95% CI 0.50–1.23). Test for subgroup difference (table 2) was significant for baseline SDB severity (p<0.01).

Functional independence

A meta-analysis was performed on 17 trials that measured functional independence among 1111 patients (figure 2). Most trials used the Barthel Index (n=13) or its Korean modified version (n=1), while others used the subscale of the Utrecht Scale for Evaluation of Rehabilitation (n=1), the Functional Independence Measure (n=1) or an unspecified activities of daily living scale (n=1). PAP therapy may result in a slight increase in functional independence in post-stroke SDB patients when compared with control (g=0.45, 95% CI 0.01–0.88; p=0.04), with considerable heterogeneity (I^2=88%, p<0.01). The 95% PI values ranged from −1.47 to 2.36, indicating that PAP therapy may not significantly improve cognition compared with a comparator in future studies conducted under similar conditions.

Our sensitivity analysis revealed no statistically significant difference (g=0.01, 95% CI −0.19–0.22; p=0.90), but a reduction in statistical heterogeneity (I^2=0%; p=0.93) after removal of eight trials conducted in Chinese populations [59, 61–63, 65–68]. Subgroup analyses (supplementary figures S17–S21) showed statistically significant improvement in functional independence in studies that used PAP for ⩾4 h per night (g=0.63, 95% CI 0.11–1.16). Test for subgroup difference (table 2) was insignificant all effect modifiers. However, meta-regression analysis revealed that publication year was a significant moderator (p=0.04), such that the most recent trials had a greater effect size in terms of improving functional independence than earlier trials (table 3).

Daytime sleepiness

A meta-analysis was performed on 11 trials that measured daytime sleepiness among 627 patients (figure 2), with nine trials utilising the Epworth Sleepiness Scale and two using the Stanford Sleepiness Scale. PAP therapy may result in a large reduction in daytime sleepiness in post-stroke SDB patients when

TABLE 3 Results of random effects univariate meta-regression on neurological deficit, functional independence and daytime sleepiness

	Neurological deficit				Functional independence				Daytime sleepiness			
	β	SE	95% CI	p-value	β	SE	95% CI	p-value	β	SE	95% CI	p-value
Mean age	0.03	0.03	−0.04–0.09	0.44	−0.01	0.02	−0.03–0.06	0.61	−0.003	0.03	−0.06–0.05	0.92
Proportion of males	0.03	0.02	−0.12–0.07	0.23	0.001	0.01	−0.03–0.03	0.93	−0.06	0.02	−0.10– −0.01	0.01*
Sample size	−0.004	0.01	−0.02–0.01	0.48	0.01	0.01	−0.004–0.03	0.16	−0.02	0.01	−0.04–0.002	0.08
Year of publication	−0.08	0.04	−0.17–0.02	0.11	0.08	0.04	0.004–0.16	0.04*	−0.12	0.07	−0.26–0.02	0.08

*: p<0.05.

compared with control (g= −0.96, 95% CI −1.56– −0.37; p<0.01), with considerable heterogeneity (I^2=88%, p<0.01). The 95% PI values ranged from −3.22 to 1.29, indicating that PAP therapy may not reduce daytime sleepiness considerably compared with a comparator in future studies conducted under comparable conditions.

Our sensitivity analysis revealed no statistically significant difference in daytime sleepiness (g= −0.53, 95% CI −1.13–0.08; p=0.09), but a reduction in statistical heterogeneity (I^2=78%, p<0.01) after removal of five trials conducted in Chinese populations [58, 59, 65–67]. Subgroup analyses (supplementary figures S22–S26) showed statistically significant reduction in daytime sleepiness in studies with >6 months follow-up period (g= −0.91, 95% CI −1.24– −0.58), with PAP adherence of ⩾4 h per night (g= −1.37, 95% CI −2.05– −0.70) and using the auto-CPAP device (g= −0.88, 95% CI −1.32– −0.43). Test for subgroup difference (table 2) was significant for nightly PAP adherence (p<0.01) and type of PAP device used (p=0.002). Meta-regression analysis revealed that the proportion of males was a significant moderator (p=0.01), indicating that the effect size of PAP therapy on daytime sleepiness will reduce by 0.06 with every 1% increase in the proportion of male participants (table 3).

Depression

A meta-analysis was performed on seven trials that measured depression among 317 patients (figure 2), with two trials using the Patient Health Questionnaire-9, one using the Beck Depression Inventory, two using the subscale of the Hospital Anxiety and Depression Scale, one using the Hamilton Depression Rating Scale, and one using the Montgomery–Asberg Depression Rating Scale. There was an insignificant reduction in depression in post-stroke SDB patients that used PAP therapy when compared with control (g= −0.56, 95% CI −2.15–1.02; p=0.49), with considerable heterogeneity (I^2=95%, p<0.01).

Our sensitivity analysis still showed no statistically significant difference in depression (g=0.34, 95% CI −0.64–1.31; p=0.50), but a reduction in statistical heterogeneity (I^2=84%, p<0.01), after removal of two trials conducted in Chinese populations [66, 67]. Subgroup analyses (supplementary figures S27–S31) showed a statistically significant subgroup difference (table 2) for nightly PAP adherence (p=0.03), stroke phase (p<0.01) and baseline SDB severity (p<0.01).

Sensitivity analysis detected one heterogenous study [66] from the analysis of cognition, functional independence, daytime sleepiness and depression. The scoring metrics used by this study deviate from the original scale but this was addressed using standardised mean difference. Additionally, the standard deviation values reported were very small, causing a strong and outlying effect. However, this is not a valid reason for study exclusion.

Publication bias

Funnel plots (supplementary figure S32) were only produced for neurological deficit, functional independence and daytime sleepiness as other outcomes lack studies (<10) for sufficient power [50]. Visual inspection of funnel plots suggests no publication bias as studies were mainly missing at the lower portion of the plot that favours an intervention effect [50]. Egger's regression test yielded insignificant results for neurological deficit (p=0.88), functional independence (p=0.85) and daytime sleepiness (p=0.86), indicating no asymmetry.

Overall quality of evidence

The GRADE assessment for overall quality of evidence is summarised in supplementary table S9. Calculations were made to obtain the optimal information size using α and β error thresholds of 0.05 and 0.8, respectively, for objective assessment of imprecision [46].

The overall certainty of the evidence for the reduction in recurrent vascular events was high despite being weighed down by imprecision arising from the rare occurrence of events. This finding was rated of critical importance as high certainty can be placed in the deployment of PAP therapy to decrease comorbid conditions and death of patients.

Findings of neurological deficit, functional independence and daytime sleepiness were of low certainty due to the high risk of bias and heterogeneity. However, these findings were deemed to be of importance for future research due to the clear benefit in statistical results and their relevance to stroke recovery. The overall certainty was rated very low for cognition and depression, which were downgraded for a high risk of bias, inconsistency and indirectness. Depression was further downgraded for imprecision due to insufficient sample size.

Discussion

This systematic review and meta-analysis aimed to determine the effectiveness of PAP therapy in decreasing recurrent vascular events and improving the health outcomes of post-stroke SDB patients.

Discussion of main findings

The pooled analysis revealed clear benefits of PAP in reducing recurrent vascular events. It was previously hypothesised that treatment of SDB could reduce cardiovascular risk, but this was never confirmed through a meta-analysis [27, 30]. Although event rates were low in the included studies, the pooled analysis strongly supports this hypothesis. This finding is also congruent with past observational studies [69, 70] and the ability to prevent further cardiovascular harm by 43% was regarded to be of critical importance in clinical decision making. As this effect is consistent over time, even up to the follow-up period of 5 years [22], clinicians can be confident that prescribing PAP is beneficial in reducing recurrent vascular events.

PAP therapy may be beneficial for all secondary outcomes, with a statistically significant effect for most outcomes except for depression. However, the high levels of heterogeneity create uncertainty in the findings. Heterogeneity was not fully explained through sensitivity, subgroup and meta-regression analyses. Subgroup analyses highlighted greater treatment benefits with PAP therapy initiated during the non-acute phase of stroke, which is surprising, considering that enhanced neuroplasticity in the early post-stroke phase should allow improved treatment response [8]. The differences in baseline severity of stroke could have confounded analysis and reduce the demonstrated effect [71]. Varying degrees of stroke severity or deficits may influence tolerance towards PAP use [72]. Yet, the investigation could be difficult as baseline stroke severity and impairment were not reported in some studies, and were excluded if conditions were severe [26, 55, 73]. In addition, in the present meta-regression results, year of publication and proportion of males were significant covariates for functional independence and daytime sleepiness, respectively. As the p-values are close to the threshold for statistical significance, the significance of the significant effects should be interpreted with caution, as this finding could be attributable to chance and may have no clinical significance. To acquire more conclusive results, additional research is required.

Our meta-analysis demonstrated non-statistically significant improvement in depression after PAP therapy. Several factors may explain this finding, including the high rate of participation refusal and study attrition. Patients with post-stroke depression were less likely to participate in treatment [74], substantiated by the lack of participants with depression in studies showing no beneficial PAP therapy effect [26]. Upfront rejection for study participation was >50% among some included studies [25], potentially missing depressed patients. Additionally, the mechanism of post-stroke depression may not be solely influenced by the biological damage of stroke or SDB, but may also be influenced by the psychosocial impact of the disease [75]. As treatment with PAP therapy may only address SDB-related damage, individualised psychiatric evaluation and treatment with antidepressants and/or psychotherapy may be required [74].

Factors influencing intervention effect

Subgroup analyses revealed a diminishing effect of PAP therapy towards neurological deficit and functional independence over time, but remained effective in decreasing daytime sleepiness and recurrent vascular events over prolonged periods. There are two possible reasons for this diminishing effect on neurological and functional recovery. First, recruitment of participants may be independent of their baseline condition, whereby some may have achieved maximum recovery before the intervention [25]. Next, the ceiling effect observed with the Barthel Index could result in the phenomenon of accelerated neurological and functional recovery [76, 77], which stagnates beyond the threshold that could be achieved by the usual care and rehabilitation provided. However, PAP therapy remains effective for daytime sleepiness and recurrent vascular events as SDB persists chronically post-stroke, thus demanding indefinite PAP therapy use as treatment rather than cure [78].

This review found that studies with the poorest PAP adherence of 1.4 h per night reported poor treatment outcomes that favour the control group [26, 55], whereas treatment for >4 h a night consistently showed better health outcomes. This demonstrated a potential dose–response relationship between duration of PAP therapy at night and post-stroke neurological deficit, cognition, functional independence, daytime sleepiness and depression. In the general SDB population, up to 7.5 h of PAP should be used per night before improvements in outcomes are observed [79]. This dose–response relationship is likely associated with the ability to achieve proper sleep. However, SDB disrupts the sleep cycle by stimulating frequent awakening, disrupting neuronal recovery [80] and increasing cardiovascular risk [81]. Therefore, the minimum effective dose of PAP is likely associated with the ability to achieve proper and sufficient sleep cycles, but the optimal duration of use in post-stroke patients remains unclear.

Four device variations, *i.e.* CPAP, auto-CPAP, nasal CPAP and bi-PAP, were explored in this review. The findings suggested that auto-CPAP produced the best effect, while the effect may vary for nasal CPAP and CPAP. Only one study explored bi-PAP and no included study used EPAP or adaptive servo-ventilation (ASV) devices. The higher cost of bi-PAP [82] and the novelty of EPAP could explain the lack of research interest [83]. ASV is a promising approach that provides smart breathing support through constant monitoring and automatic re-adjustment of pressure support, but is lacking investigation for post-stroke SDB patients [84]. Future research should proceed with care, as the SERVE-HF trial exploring the effectiveness of ASV for heart failure patients cautioned an increased risk of cardiac death [85]. Currently, an ongoing multicentre RCT (eSATIS) exploring the effectiveness of ASV for post-stroke SDB patients is expected to be completed by November 2022 (ClinicalTrials.gov: NCT02554487). Although expected to be more expensive than the CPAP device, these advanced PAP modalities could improve comfort and adherence, and decrease overall healthcare cost and time required for laboratory SDB diagnosis [84].

Strengths and limitations

This systematic review and meta-analysis of RCTs demonstrated the effect of PAP therapy on post-stroke patients with SDB. A comprehensive search strategy was employed on both English and Chinese literature, which enhances the generalisability of findings to other ethnic groups than only the Western population. However, there were some limitations in this review. First, high levels of heterogeneity were detected across secondary outcomes and all included studies were of high risk of bias, thus reducing the certainty of evidence. Second, Chinese studies mostly report positive findings but lack detailed reporting, making it difficult to highlight and replicate critical factors behind therapy success. Furthermore, the lack of detailed reporting resulted in an unclear risk for allocation concealment, blinding of outcome assessors and selective reporting, which could jeopardise the internal validity of the trial. Indeed, our sensitivity analysis revealed that the Chinese studies tended to have inflated results, which may bias the true effect away from the null. Third, adherence data of included studies could be based on subjective estimates of nightly use. This method of data gathering could give rise to recall and/or social desirability bias [86] and could be addressed by utilising PAP devices that allow machine recording of adherence data. Finally, it was also not determined whether the included participants had SDB preceding their stroke incident in all studies and this will likely remain a challenge for future trials to detect due to the low health-seeking rates for this condition [87]. However, this information is crucial to inform clinical decisions on the proper timing to begin or resume PAP therapy for those with pre-existing SDB.

Contribution to knowledge and implications for clinical practice and future research

This review is the first among its peers to meta-analyse multiple post-stroke SDB outcomes using only RCTs. Based on the findings of this review, institutions should consider treating post-stroke SDB patients with PAP therapy to reduce recurrent vascular events risk and improve the prospect of recovery in other health outcomes. Potential health benefits heavily outweigh any risk or adverse effect and improved outcomes were found in patients with mild-to-moderate SDB treated in the non-acute phase of the stroke. Compliance is crucial and at least 4 h of usage per night should be reinforced until further studies ascertain an optimal usage duration. This review provides three important directions for future research, including 1) optimal duration of PAP use and period of treatment; 2) identifying the necessity for urgent diagnosis and treatment of SDB; and 3) RCTs utilising sham-controlled PAP devices as placebo and proper blinding of outcome assessor to reduce risk of bias. Finally, future trials should adhere to the guidelines outlined in the CONSORT (Consolidated Standards of Reporting Trials) statement (www.consort-statement.org) to improve the quality of reports.

Points for clinical practice

- PAP has been shown to reduce recurrent vascular events and have significant beneficial effects on neurological deficit, cognition, functional independence and daytime sleepiness in post-stroke patients with SDB.

Questions for future research

- What is the optimal duration of PAP use and period of treatment?
- What is the necessity for urgent diagnosis and treatment of SDB?

Conclusions

PAP therapy was effective in reducing recurrent vascular events. The beneficial effects were also observed in other health outcomes but should be interpreted with caution in the context of the high heterogeneity observed. Despite the unexplained heterogeneity, PAP therapy can be confidently prescribed based on its clear positive effect in reducing recurrent vascular events and statistically significant effects on other health outcomes. The subgroup analyses allow a better appreciation of adherence reinforcement and highlight the phenomenon of improved outcomes for patients with mild-to-moderate SDB treated in the non-acute phase of the stroke. PAP therapy should be initiated for post-stroke SDB patients while ensuring a minimum of 4 h of nightly use until further studies determine the minimum effective dose. Considering the high heterogeneity levels and overall risk of bias, more RCTs with rigorous methodology will be required to supplement current findings.

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Data availability: Data related to this review can either be found in the supplementary material or is available upon request from the corresponding author: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

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