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The effectiveness of supplemental oxygen and high-flow nasal cannula therapy in patients with obstructive sleep apnea in different clinical settings: A systematic review and meta-analysis

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HIGHLIGHTS

- Oxygen therapy reduced apnea-hypopnea index by 31% and increased oxyhemoglobin saturation by 5% versus baseline.
- Continuous positive airway pressure therapy was more effective in decreasing apnea-hypopnea index than oxygen therapy by 53%.
- Both oxygen and continuous positive airway pressure therapy had similar effectiveness in increasing oxyhemoglobin saturation.
- High-flow nasal therapy reduced apnea-hypopnea index by 36%, but did not substantially increase oxyhemoglobin saturation.

ARTICLE INFO

Keywords:
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Obstructive sleep apnea
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ABSTRACT

Study objective: To evaluate the effectiveness of supplemental oxygen therapy and high-flow nasal cannula (HFNC) therapy in patients with obstructive sleep apnea (OSA) in different clinical settings to assess its application to surgical patients in the postoperative setting.
Design: A systematic search was conducted on MEDLINE and other databases from 1946 to December 16th, 2021. Title and abstract screening were conducted independently, and the lead investigators resolved conflicts. Meta-analyses were performed using a random-effects model and are presented as mean difference and standardized mean difference with 95% confidence intervals. These were calculated using RevMan 5.4.
Patients: 1395 and 228 OSA patients underwent oxygen therapy and HFNC therapy respectively.
Interventions: Oxygen therapy and HFNC therapy.
Measurements: Apnea-hypopnea index (AHI), oxyhemoglobin saturation (SpO_2), cumulative time with $SPO_2 <$ 90% (CT90).
Main results: Twenty-seven oxygen therapy studies were included in the review, with ten randomized controlled trials (RCT), seven randomized crossovers, seven non-randomized crossovers, and three prospective cohorts. Pooled analyses showed that oxygen therapy significantly reduced AHI by 31% and increased SpO_2 by 5% versus baseline, and CPAP significantly reduced AHI by 84%, and increased SpO_2 by 3% versus baseline. CPAP was 53% more effective in reducing AHI than oxygen therapy, but both treatments had similar effectiveness in increasing SpO_2. Nine HFNC studies were included in the review, with five prospective cohorts, three randomized crossovers, and one RCT. Pooled analyses showed that HFNC therapy significantly reduced AHI by 36% but did not substantially increase SpO_2.
Conclusions: Oxygen therapy effectively reduces AHI and increases SpO_2 in patients with OSA. CPAP is more effective in reducing AHI than oxygen therapy. HFNC therapy is effective in reducing AHI. Although both oxygen

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therapy and HFNC therapy effectively reduce AHI, more research is needed to draw conclusions on clinical outcomes.

1. Introduction

In the surgical setting, patients with obstructive sleep apnea (OSA) may have increased upper airway collapsibility affecting ventilation [1] and increased sensitivity to sedation from anesthetics and opioids [2]. Surgical patients with OSA have a high risk for postoperative complications, including cardiac events, desaturation, and transfer to the intensive care unit [3–6]. Continuous positive airway pressure (CPAP) is the gold standard treatment for moderate to severe OSA and effectively reduces the risk of cardiovascular events [6–10]. Evidence has shown that CPAP effectively reduces apnea-hypopnea index (AHI) and length of hospital stay (LOS) in the postoperative setting [10,11]. Despite the benefits of CPAP in patients with OSA, there may not be sufficient time to identify and treat newly diagnosed OSA patients in the surgical setting [12]. Patients also experience discomfort when using CPAP, resulting in a low to moderate adherence rate [13–15].

In these scenarios, supplemental oxygen therapy may be an acceptable alternative to CPAP in the surgical setting [16], but clinical considerations have been raised when using supplemental oxygen therapy. Supplemental oxygen therapy may prolong the duration of apneas, causing hypoventilation [17]. Notably, supplemental oxygen therapy may also mask the ability of pulse oximetry to detect hypoventilation [18]. One recent randomized controlled trial (RCT) found that 11 % of surgical patients with OSA receiving postoperative supplemental oxygen therapy were at risk of experiencing increased carbon dioxide (CO_2) retention and hypercapnia [16].

The emergence of high-flow nasal cannula (HFNC) therapy has been used as an alternative for CPAP non-adherent patients. HFNC delivers warm, humidified air through a nasal cannula at high flow rates of up to 60 L/min. This high flow rate may increase end-expiratory pharyngeal pressure up to 3 cm H_2O, decreasing the force required to alleviate airway collapse [19]. Using a nasal cannula interface in contrast to the CPAP mask may provide a more comfortable experience for patients during sleep [20]. To date, there has been no systematic review of the utilization of HFNC in patients with OSA.

Due to hypoxemia in the post-anesthesia care unit or the wards, surgical patients with OSA often receive supplemental oxygen therapy. This systematic review and meta-analysis aimed to evaluate the effectiveness of supplemental oxygen and high-flow nasal cannula therapy on AHI and oxyhemoglobin saturation (SpO_2) in patients with OSA in different clinical settings to assess its application in the postoperative setting.

2. Materials & methods

2.1. Protocol and registration

The systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; #CRD42022335061). This study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [21].

2.2. Search strategy

An information specialist (ME) conducted a systematic and structured literature search. All searches were conducted from 1946 on December 16th, 2021, using the Ovid platform for the following databases: MEDLINE, MEDLINE Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations, Embase/Embase Classic, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews.

Preliminary searches were conducted, and full-text literature was considered for potential keywords and appropriately controlled vocabulary terms (such as Medical Subject Headings (MeSH) for Medline and EMTREE descriptors for Embase). The Yale MeSH Analyzer was used to assess target citations [22]. The search strategy concept blocks were built on "Obstructive Sleep Apnea" AND "Oxygen Therapy," with each component being fleshed out with controlled vocabularies, text word terms and synonyms. Results were limited to the English language, humans, and adults. Conference abstracts were removed at the source where possible.

Supplemental searching was conducted using ClinicalTrials.Gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and citation searching via Google Scholar and PubMed. The reference lists of included studies were performed to identify any additional articles missed in the initial yield. Continued literature surveillance was conducted throughout March 30th, 2022. The complete detailed Medline search strategy is in Table A1.

2.3. Study selection and data extraction

Using the software Rayyan, title and abstract screening and full-text screening were independently completed by two pairs of reviewers (MR, KZ) and (BR, MR), respectively. Inclusion criteria for selected studies were as follows: 1) patients 18 years old or older; 2) diagnosed or at risk of OSA by screening questionnaires such as the STOP-Bang [23]; 3) received supplemental oxygen therapy or HFNC therapy as their primary study intervention; 4) reported at least one of the following primary outcomes: total number of apneas and hypopneas per hour (AHI), mean overnight oxyhemoglobin saturation (SpO_2), and cumulative time spent when $SpO_2 < 90\%$ (CT90); 5) secondary outcomes included clinical outcomes (treatment adherence, adverse events, or postoperative complications); and 6) RCTs, prospective, and retrospective cohort studies. Studies were excluded if: 1) patients had predominant central sleep apnea (CSA); 2) prior surgery for OSA; and 3) non-English publications. Data extracted from selected studies included author, year of publication, country, study design, sample size, age, gender, body mass index (BMI), treatment adherence, AHI, oxygen desaturation index (ODI), and mean overnight SpO_2. Data extraction was performed independently by two authors (BR, MR). Attempts were made to obtain any missing data from studies by contacting the corresponding author. Any differences in extracted data were reviewed by another author (MN), and a consensus was reached via discussion.

2.4. Assessment of study quality and bias

The quality and bias of included studies were independently assessed by two reviewers (MR, KZ) utilizing the Newcastle-Ottawa Scale (NOS) for cohort studies and the Joanna Briggs Institute's (JBI) critical appraisal tool for RCTs [24,25]. The NOS checklist assesses studies through three primary arms: participant selection, comparability, and outcomes. Regarding participant selection and outcomes, a maximum of one star (*) was awarded to each criterion fulfilled within each arm, while a maximum of two stars (**) was awarded to criteria fulfilled in the comparability category. Non-randomized crossover studies were classified as cohort studies for this analysis. The JBI checklist assesses studies through four primary arms: study design, population, outcomes, and statistical analysis. Each component was evaluated using the following options: yes, no, unclear, or not applicable. After an independent assessment of the studies, the reviewers met to identify any disagreements resolved by the senior author (FC).

2.5. Statistical analysis

Descriptive statistics were presented as mean with standard deviation (SD). The principal summary measure, which is the impact of the intervention (oxygen therapy, CPAP therapy, HFNC therapy) was measured by weighted mean difference with a 95% confidence interval (CI) for continuous outcomes. The Inverse Variance method was used to combine continuous events. Meta-analysis of RDI was pooled with AHI data when AHI was not reported. A random-effects model was used to calculate the mean difference (MD) and standardized mean differences (SMD) for AHI or RDI, and SpO_2 at post-treatment (post-treatment - baseline). These SMD values (SD = 1) were entered into a random-effects model to compare the post-treatment of oxygen therapy and CPAP groups. Predictive intervals were calculated using the number of studies, 95% CI upper value, and the Tau-squared statistic (Tau [2]). The probability of the benefit from the treatment was calculated using Z-score table statistics.

Publication bias was assessed using Egger's test and Begg's test. The I^2 statistic was used to examine heterogeneity for each significant outcome. Sensitivity or influential analysis was performed to explore the heterogeneity, where one study was excluded each time to recalculate I^2. Meta-analyses were conducted using RevMan 5.4, and a two-tailed *P*-value <0.05 was considered statistically significant.

3. Results

This study adhered to the Cochrane Handbook for Systematic Reviews of Interventions and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when developing the database search strategies [26,27]. Our initial database search yielded 9414 studies, with 7290 after removing duplicates (Fig. 1). After screening, 7189 articles were excluded, leaving 101 for full-text review. Following a full-text review, 65 articles were excluded. Reasons for exclusion included: wrong study design ($n = 4$), wrong intervention ($n = 28$), wrong study outcome ($n = 8$), wrong study population ($n = 21$), unable to locate article ($n = 1$), and articles reporting on duplicate clinical trials ($n = 3$). Thirty-six studies were included in the systematic review, and 25 studies were included in the meta-analysis.

3.1. Study and patient characteristics

Study characteristics and demographics are shown in Table 1. Twenty-seven studies included 1395 OSA patients in the supplemental oxygen therapy group. The mean age of these patients was 52.8 ± 10.3

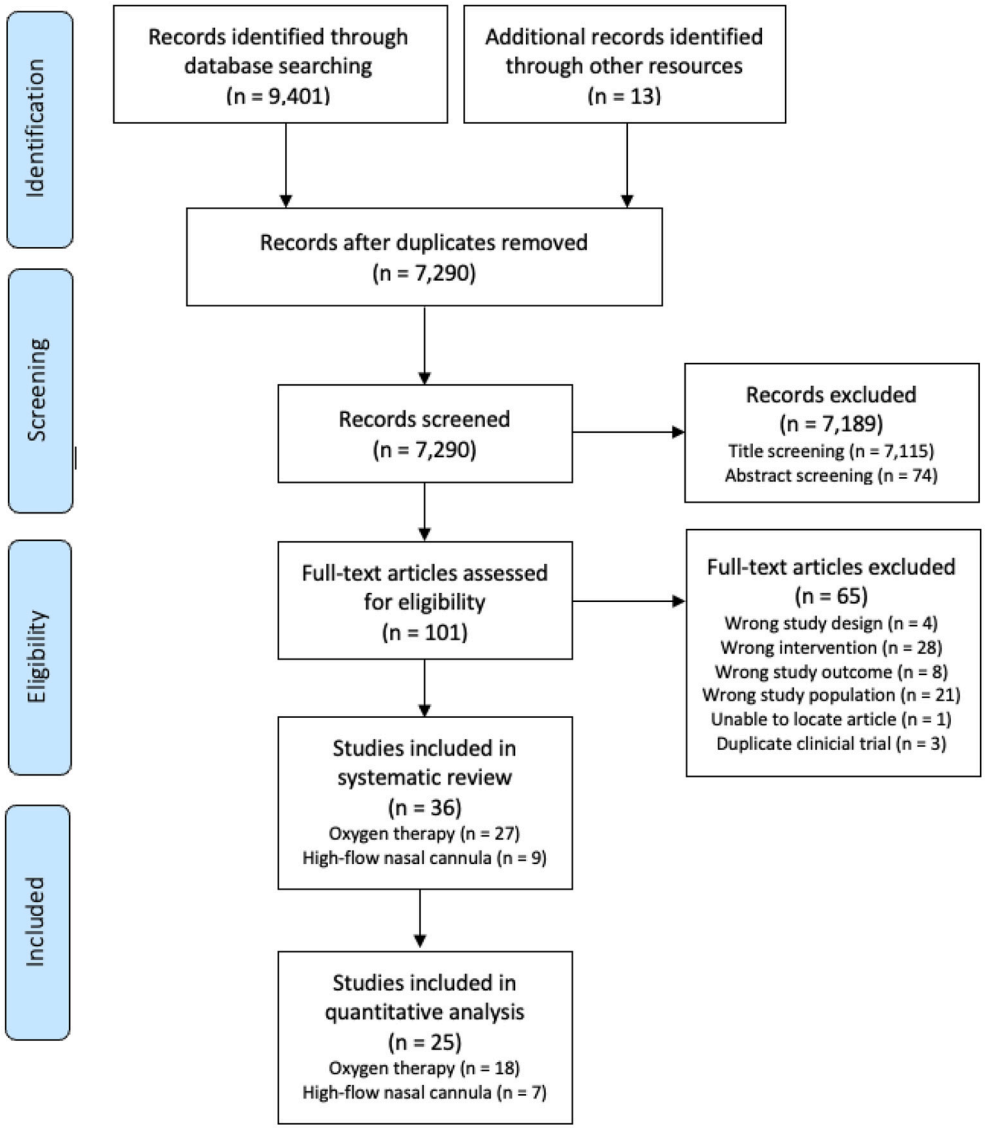

Fig. 1. PRISMA flow diagram.

Table 1
Study demographics.

1st author year, country	Study design	OSA severity (n)			Age (years) mean ± SD	Male n (%)	BMI (kg/m^2) mean ± SD	Patient population
		mild OSA	moderate-severe OSA	Total (N)				
O_2 therapy vs. air								
Kearley 1980, USA [46]	non-randomized crossover	NR	NR	11	61 ± 10	10(91)	25 ± 7	hospital & clinic patients
Goldstein 1984, Canada [47]	non-randomized crossover	0	3	3	NR	NR	NR	hospital rehab patients
Spier 1984, Canada [42]	randomized crossover	NR	NR	2	26(NR)	1(100)	18(NR)	NR
Alford 1986, USA [17]	randomized crossover	0	20	20	57 ± 8	20(100)	NR	clinic patients
Gold 1986, USA [48]	non-randomized crossover	NR	NR	8	50 ± 8	7(88)	NR	sleep clinic
Block 1987, USA [44]	non-randomized crossover	2	16	18	50 ± 12	20(100)	31 ± 5	heavy snorers
Marrone 1992, Italy [39]	randomized crossover	0	6	6	50 ± 14	3(50)	34 ± 7	NR
Pokorski 2000, Poland [45]	non-randomized crossover	0	5	5	41 ± 12	5(100)	38 ± 6	sleep clinic
Friedman 2001, USA [49]	non-randomized crossover	0	phase 1 = 43, phase 2 = 21	43	42(NR)	35(81)	NR	NR
Teramoto 2003, Japan [40]	randomized crossover	0	24	24	54 ± 4	19(79)	29 ± 2	NR
Wellman 2008, USA [43]	non-randomized crossover	0	12	12	51 ± 9	11(92)	31 ± 3	sleep clinic
Liao 2017, Canada [16]	RCT	36	32	68	62 ± 11	79(64)	33 ± 8	surgical patients
Turnbull 2019, UK [38]	randomized crossover	0	25	25	63 ± 7	21(84)	35 ± 7	NR
Tan 2021, China [37]	randomized crossover	0	34	34	48 ± 7	34(100)	26 ± 3	subjects from Tibet
Waltz 2021, Canada [34]	RCT	0	23	23	48 ± 10	21(91)	32 ± 5	NR
O_2 therapy vs. CPAP								
Phillips 1990, USA [41]	randomized crossover	3	5	8	57 ± 14	8(100)	33 ± 10	sleep clinic
Loredo 2006, USA [30]	RCT	0	63	63	47 ± 10	50(79)	32 ± 6	sleep clinic
Mills 2006, USA [31]	RCT	0	50	50	47 ± 10	41(82)	32 ± 6	NR
Norman 2006, USA [33]	RCT	0	46	46	48 ± 10	37(80)	30 ± 5	NR
Bardwell 2007, USA [35]	RCT	0	38	38	46 ± 10	33(87)	30 ± 6	NR
Lim 2007, USA [32]	RCT	0	46	46	48 ± 10	NR	31 ± 11	NR
Frohnhofen 2009, Germany [50]	PC	NR	NR	200	81 ± 6	77(39)	NR	NR
Lewis 2017, USA [28]	RCT	0	318	318	63 ± 7	233(73)	34 ± 6	cardiology clinic
Beaudin 2019, Canada [36]	RCT	0	52	52	50 ± 8	46(89)	31 ± 5	sleep clinic
Magnusdottir 2021, USA [29]	RCT	0	241	241	63 ± 7	178(74)	34 ± 6	cardiology clinic
O_2 therapy vs. no Rx								
Kumagai 2008, Japan [51]	PC	NR	NR	11	64 ± 4	10(91)	25 ± 4	PD unit
Wang 2018, Australia [52]	PC	NR	NR	20	58 ± 11	14(70)	31 ± 9	sleep clinic
HFNC therapy								
McGinley 2007, USA [58]	randomized crossover	3	8	11	50 ± 17	6(55)	31 ± 14	sleep clinic
Nilius 2010, Germany [53]	PC	NR	NR	54	51 ± 10	42(78)	28 ± 4	sleep clinic
Sowho 2015, Australia [20]	randomized crossover	13	15	28	51 ± 10	3(30)	32 ± 8	NR
Haba-Rubio 2012, Switzerland [54]	PC	0	10	10	57 ± 11	10(100)	NR	stroke unit
Ho 2020, Taiwan [55]	PC	0	10	10	74 ± 13	8(73)	24 ± 3	stroke unit
Nakanishi 2020, Japan [56]	PC	0	11	11	68 ± 12	7(88)	25 ± 5	stroke unit (suspected SDB)
Yan 2021, China [57]	PC	3	5	8	46 ± 13	47(85)	27 ± 3	sleep clinic
Yu 2021, Taiwan [59]	randomized crossover	9	47	56	52 ± 17	21(75)	27 ± 6	sleep clinic
Tsai 2022, Singapore [60]	RCT	NR	NR	40	49 ± 15	21(53)	43 ± 6	surgical patients

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula therapy; NR, not reported; OSA, obstructive sleep apnea; O_2, oxygen; PC, prospective cohort; PD, peritoneal dialysis; rehab, rehabilitation; Rx, treatment intervention; SD, standard deviation; SDB, sleep-disordered breathing; UK, United Kingdom; USA, United States of America.

years old; 72.6% were males with BMI of 30.6 ± 4.2 kg/m^2. There were ten RCTs [16,28–36], seven randomized crossovers [17,37–42], seven non-randomized crossovers [43–49], and three prospective cohorts [50–52]. Fifteen studies had two comparison groups that compared supplemental oxygen therapy to breathing air during sleep [16,17,34,37–40,42–49]. Nine studies had three intervention arms: five studies compared placebo-CPAP oxygen delivery, CPAP, and sham-CPAP [30–33,35]; two studies compared oxygen therapy via nasal cannula delivery, CPAP, and healthy lifestyle education [28,29]; and two studies compared oxygen therapy via nasal cannula delivery, CPAP, and breathing air [36,41]. One study compared oxygen therapy to CPAP alone [50], and two studies investigated supplemental oxygen therapy with no comparison group [51,52].

Nine studies included 228 OSA patients in the HFNC therapy group. The mean age was 55.3 ± 9.4 years old; 72.3% were males with a mean BMI of 29.6 ± 6.0 kg/m^2. Five studies were prospective cohorts [53–57], three were randomized crossover [20,58,59], and one was a RCT [60]. Three studies compared HFNC to CPAP therapy [20,59,60], one compared HFNC therapy to air [58], while the remaining studies only had a HFNC intervention arm [53–57]. All studies reported AHI or RDI, oxygenation, or clinical outcomes.

3.2. Effect of oxygen therapy on AHI/RDI and oxygenation

Ten studies (228 OSA patients) reported the AHI or RDI of subjects who received oxygen therapy (Table B1) [16,37,38,40,43,45,48,49,51,52]. The pooled analysis showed that patients with OSA had a significantly decreased mean AHI from a baseline value of 41.4 ± 16.5 events per hour to 28.6 ± 12.2 events per hour after oxygen therapy (MD: -11.2; 95% CI: −18.7 to −3.7; $P = 0.003$). The SMD was −0.66 (95% CI, −1.1 to −0.22, $P = 0.004$, $I^2 = 78\%$) (Fig. Error! Reference source not found.). Eleven studies (220 OSA patients) reported SpO_2 of subjects provided with oxygen therapy [16,17,34,37,40,43,45,48,51,52]. The pooled analysis showed that patients with OSA had a significant increase in SpO_2 from a baseline value of 90% ± 4% to 95% ± 2% after oxygen therapy (MD: 4.0; 95% CI: 2.1 to 5.9; $P < 0.0001$). The SMD was 1.6 (95% CI, 0.78 to 2.5, $P < 0.001$, $I^2 = 92\%$) (Fig. 2B). Essentially, oxygen therapy significantly reduced AHI by 31% and increased SpO_2 by 5% compared to baseline.

3.3. Comparison of oxygen therapy vs. CPAP on AHI/RDI and oxygenation

Five studies (173 OSA patients) compared the effects of oxygen

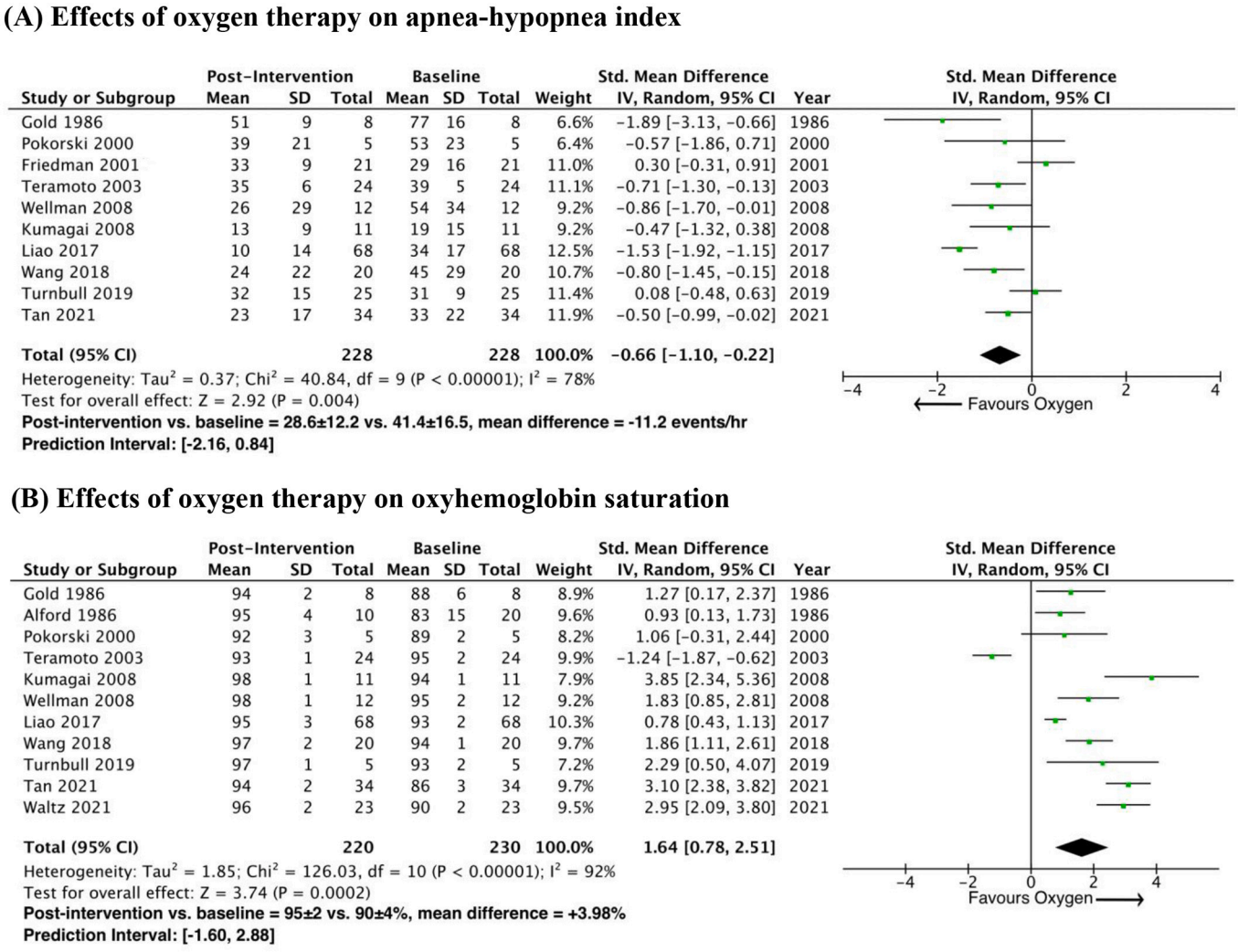

Fig. 2. Meta-analysis of oxygen therapy on apnea-hypopnea index and oxyhemoglobin saturation. Fig. 2A Effects of oxygen therapy on apnea-hypopnea index. Fig. 2B. Effects of oxygen therapy on oxyhemoglobin saturation.

Abbreviations: Chi^2, Chi-squared statistic; CI, confidence interval; df, degrees of freedom; I^2, variation attributable to heterogeneity; IV, inverse variance; SD, standard deviation; Std. mean difference, standardized mean difference; Tau^2, Tau-squared estimate.

therapy (78 OSA patients) and CPAP therapy (95 OSA patients) on the AHI or RDI (Table B2) [31,33,35,36,41]. The pooled analysis showed that patients with OSA had a significantly decreased mean AHI from a baseline value of 49.0 ± 28.2 events per hour to 7.8 ± 9.3 events per hour after CPAP (MD: -39.9; 95% CI: −46.4 to −34.5; $P < 0.001$). The SMD was −2.6 (95% CI, −3.5 to −1.7, $P < 0.00001$, $I^2 = 78\%$). Notably, CPAP significantly reduced AHI by 84%.

Pooled analysis also demonstrated that CPAP significantly reduced AHI compared to oxygen therapy and was 53% more effective with a SMD of 1.6 (95% CI, 1.0 to 2.1, $P < 0.00001$, $I^2 = 54\%$ (Fig. 3A). The probability of CPAP decreasing the mean AHI compared to oxygen therapy was 94% (oxygen vs. CPAP therapy: MD: −16.5 vs. -39.9).

Five studies (171 OSA patients) compared the effects of oxygen therapy (76 OSA patients) and CPAP therapy (95 OSA patients) on the SpO_2 [32,33,35,36,41]. When comparing the effects of oxygen therapy to CPAP on SpO_2, oxygen therapy demonstrated similar effectiveness to CPAP therapy with a SMD of 0.33 (95% CI, −0.42 to 1.1, $P = 0.39$, $I^2 =$ 82%) (Fig. 3B). The probability of CPAP improving the SpO_2 versus oxygen therapy was 63% (oxygen vs. CPAP therapy: MD: 5.8% vs. 3.0%).

Four RCTs (157 OSA patients) compared the effects of oxygen therapy (70 OSA patients) and CPAP therapy (87 OSA patients) on cumulative time with $SpO_2 < 90\%$ (CT90) [31,33,35,36]. The pooled analysis showed that when oxygen therapy was compared to CPAP, both

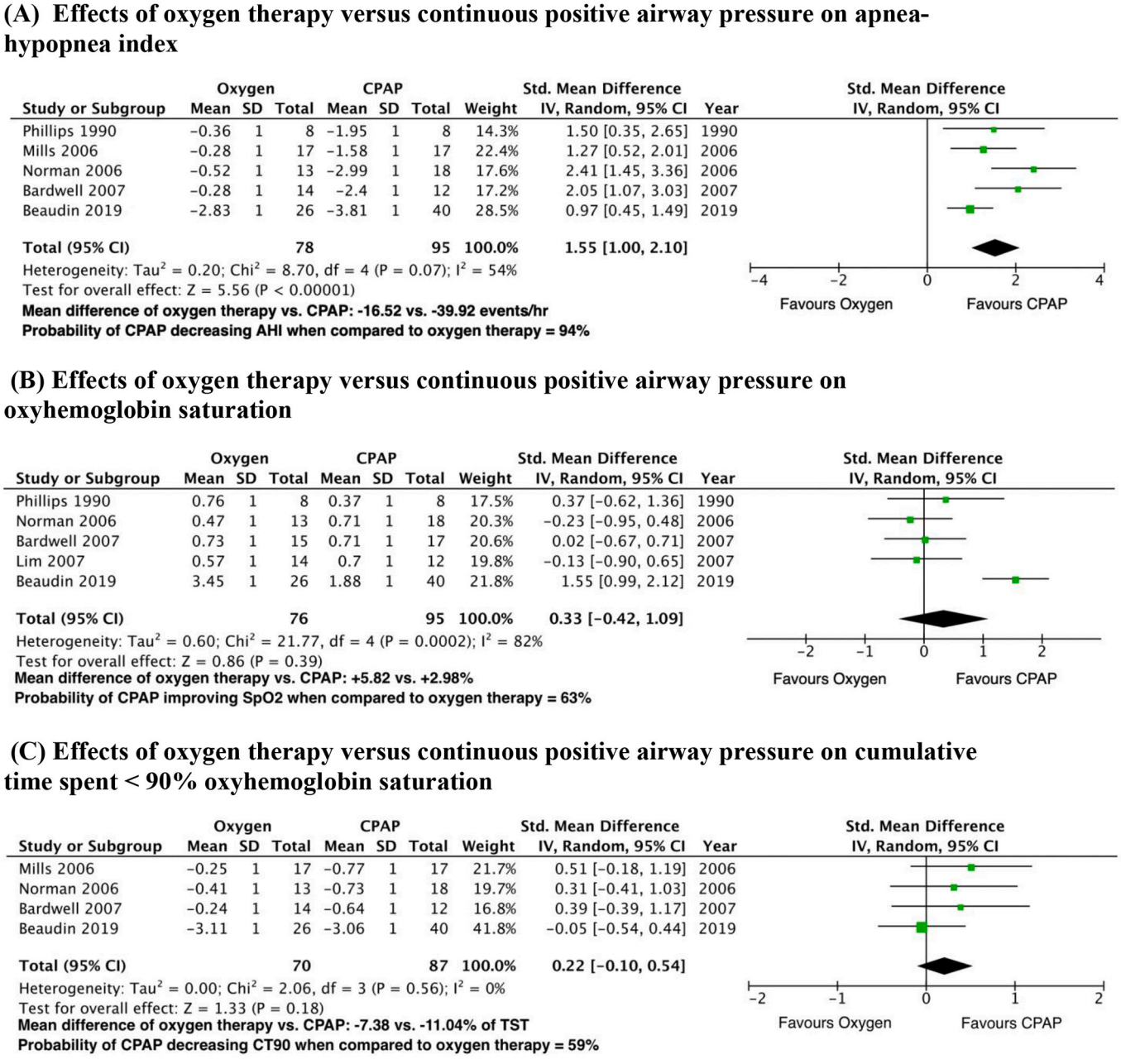

Fig. 3. Oxygen therapy and continuous positive airway pressure on apnea-hypopnea index and oxyhemoglobin saturation. Fig. 3A. Effects of oxygen therapy versus continuous positive airway pressure on apnea-hypopnea index. Fig. 3B. Effects of oxygen therapy versus continuous positive airway pressure on oxyhemoglobin saturation. Fig. 3C. Effects of oxygen therapy versus continuous positive airway pressure on cumulative time spent < 90% oxyhemoglobin saturation.
Abbreviations: Chi^2, Chi-squared statistic; CI, confidence interval; CT90, cumulative time spent with oxyhemoglobin saturation < 90%; df, degrees of freedom; I^2, variation attributable to heterogeneity; IV, inverse variance; SD, standard deviation; SpO_2, oxyhemoglobin saturation; Std. mean difference, standardized mean difference; Tau^2, Tau-squared estimate; TST, total sleep time.

treatments showed similar effectiveness in reducing CT90. The SMD was 0.22 (95% CI, −0.10 to 0.54, $P = 0.18$, $I^2 = 0$) (Fig. 3C). The probability of CPAP decreasing CT90 compared to oxygen therapy was 59% (Oxygen vs. CPAP therapy: mean difference: −7.4 vs. -11.0).

3.4. Clinically reported outcomes on supplemental oxygen therapy

Eleven studies reported CO_2 levels while using oxygen therapy (Table 2) [16,17,37,39,40,42,43,46–48,52]. A meta-analysis could not be conducted due to high variability in the methodology of the CO_2 data collection. Notably, three studies demonstrated a significant increase in CO_2 levels on oxygen therapy versus breathing air at baseline [17,39,48]. Two of these studies mainly had patients with obstructive pulmonary diseases [17,48]. Notably, Liao et al. found that 11% of surgical patients with OSA had elevated transcutaneous carbon dioxide levels ($PtCO_2$) >55 mmHg postoperatively while breathing supplemental oxygen [16].

Eight studies reported clinical outcomes for patients who underwent oxygen therapy [16,28,29,32,35,41,45,50]. In a RCT, 123 surgical patients with newly diagnosed OSA were randomized to oxygen therapy or no oxygen during postoperative nights. Seven patients receiving oxygen therapy on the first three postoperative nights experienced desaturation events, and five had inadequate pain control [16].

There were contradictory findings in various studies on psychological outcomes. Patients had significantly improved self-reported effects in the morning after the administration of supplemental oxygen therapy compared to nights with room air [45]. Two studies reported a decrease in depressive symptoms [28,35], but one reported no significant change in depressive symptoms following supplemental oxygen therapy [29]. Phillips et al. found substantial increases in immediate recall of visual memory, delayed recall of visual memory, and visual attention after supplemental oxygen therapy. Still, Lim et al. reported no significant increases in neuropsychological outcomes [32]. In one study, older adults were reported to increase daily living activities significantly after oxygen therapy [50].

Table 2
Oxygenation and carbon dioxide levels.

Author year	Patient population	Comorbidities	Total moderate-severe OSA patients (N)	O_2 therapy	O_2 flow rate (L/min)	Mean overnight SpO_2 (% sat.) mean ± SD		Patient CO_2 levels (mmHg) mean ± SD		CO_2 method	CO_2 data collection	Measuring device
						Baseline/Air	O_2	Baseline/Air	O_2			
Kearley 1980 [46]	hospital & clinic	COPD (100%)	11	nasal cannula	2	NR	NR	44 ± 8	44 (NR)	$PaCO_2$	sleep ABG at >4% oxygen desaturation	ABG
Goldstein 1984 [47]	hospital rehab	COPD (100%)	3	nasal cannula	1–2	NR	NR	NR	19 ± 3	$PtcCO_2$	10 min unchanged sleep state	Model 110 Gould
Spier 1984 [42]	NR	CF (50%) COPD (50%)	1	nasal cannula	1	84(NR)	NR	16(NR)	22 (NR)	$PtcCO_2$	5 min of resting awake stage of sleep	Hewlett-Packard 47210A
Alford 1986 [17]	clinic	asthma chronic bronchitis COPD (100%) CHF	20	face mask	4	88 ± 6	95 ± 4	45 ± 7	62 ± 1	$PaCO_2$	during apneic events >10 s	ABG
Gold 1986 [48]	sleep clinic	mild obstructive ventilatory defect extrathoracic airway obstruction	8	nasal cannula	4	83 ± 15	94 ± 2	40 ± 5	43 ± 1	$PaCO_2$	during resting awake stage of sleep	ABG
Marrone 1992 [39]	NR	none	6	nasal cannula	4–6	74 ± 13	NR	42 ± 1	59 ± 3	$PtcCO_2$	Maximum apneic $PtcCO_2$ during sleep	Hewlett-Packard 47210A
Teramoto 2003 [40]	NR	none	24	nasal cannula	1–2	95 ± 2	93 ± 1	42 ± 1	NR	$PtcCO_2$	NR	ABG
Wellman 2008 [43]	sleep clinic	none	12	nasal cannula	3–5	95 ± 2	98 ± 1	42 ± 2	42 ± 3	$EtCO_2$	average overnight	BCI
Liao 2017 [16]	surgical patients	asthma COPD (5.8%) smoker CVD[$] DM	68	nasal cannula	3	93 ± 2	95 ± 3	39 ± 8	41 ± 6	$PtcCO_2$	average overnight post-op night 1 & 3	TCM400 radiometer
Wang 2018 [52]	sleep clinic	none	20	nasal cannula	3	94 ± 1	97 ± 2	NR	40 ± 4	$PaCO_2$	average overnight	ABG
Tan 2021 [37]	Tibet subjects (high altitude)	hypertension DM	34	nasal cannula	2	86 ± 3	94 ± 2	46 ± 6	47 ± 8	$PtcCO_2$	average overnight during sleep	TCM4 radiometer

[$]includes hypertension, coronary artery disease, myocardial infarction, stroke.

Abbreviations: CF, cystic fibrosis; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CO_2, carbon dioxide; CVD, cardiovascular disease; DM, diabetes mellitus; $EtCO_2$, end-tidal carbon dioxide; NR, not reported; OSA, obstructive sleep apnea; O_2, oxygen; $PaCO_2$, partial arteriole pressure of carbon dioxide; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; Rx, treatment intervention; SD, standard deviation; SpO_2, oxyhemoglobin saturation.

3.5. Effects of high-flow nasal cannula therapy on apnea-hypopnea index and oxygenation

Five prospective cohort [53–57] and two randomized crossover studies [58,59] with 178 OSA patients received HFNC oxygen therapy (Table B3). The pooled analysis showed that patients with OSA had a significantly decreased mean AHI from a baseline value of 31.9 ± 9.9 events per hour to 20.3 ± 6.6 events per hour after HFNC therapy (MD: -10.0; 95% CI: −15.8 to −4.1; $p = 0.0008$). The SMD was −0.55 (95% CI, −0.82 to −0.28, $P < 0.0001$, $I^2 = 26\%$) (Fig. 4A).

Four prospective cohorts [54–57] and one randomized crossover study [59] (113 OSA patients) on HFNC oxygen therapy reported SpO_2 parameters. Compared to the baseline, pooled analysis of the five studies showed that patients had no statistically significant change in mean overnight SpO_2 from a baseline value of 94.0 ± 0.8% to 94.3 ± 0.7% after HFNC therapy with a SMD of 0.18 (95% CI: −0.18 to 0.54, $P = 0.32$, $I^2 = 33\%$) (MD: 0.33; 95% CI: −0.32 to 0.98; $p = 0.32$) (Fig. 4B). In summary, HFNC therapy significantly reduced AHI by 36.4% but did not substantially increase SpO_2.

3.6. Clinically reported outcomes on high-flow nasal cannula therapy

Two RCTs evaluated treatment adherence to HFNC versus CPAP [20,60]. One RCT found that adherence to HFNC therapy was significantly better than CPAP therapy on postoperative night one [60]. This contrasts with a randomized crossover study, where HFNC adherence was similar to CPAP at home [20].

Two studies reported on the side effects of HFNC versus CPAP [59,60]. One randomized crossover study found that loud noise, strong airflow discomfort, and frequent sleep awakenings were associated with HFNC [59]. The main side effect of CPAP was mask discomfort. Overall, patients perceived CPAP to be more comfortable than HFNC [59]. In contrast, another RCT reported that patients found HFNC more relaxed, less noisy, and easier to use than CPAP [60]. Four studies reported patients who withdrew consent during HFNC therapy due to discomfort [55–57,59].

3.7. Quality assessment

The NOS scores of the 15 included cohort studies [43–57] ranged from 4 to 9 out of a possible score of 9 (Table C1). Of the included prospective cohort studies, more than half of the included cohort studies did not have a good selection of a non-exposed cohort. Seven studies (47%) did not have appropriate comparability of cohorts, and some did not have robust inclusion criteria of how OSA patients were diagnosed or defined. All cohort studies scored well in the ascertainment of the exposure, demonstrated that the outcome of interest was not present at the start of the study, and assessed outcomes with sufficient follow-up duration. There was an adequate follow-up of the cohorts in most studies. The JBI critical appraisal checklist was used to assess the 21 RCTs [16,17,20,28–42,58–60], which were well-designed based on study design, population, outcomes, and statistical analysis (Table C2).

4. Discussion

This is the first systematic review and meta-analysis to evaluate the effectiveness of supplemental oxygen therapy and high-flow nasal cannula therapy as an alternative to CPAP therapy to treat patients with OSA. In this systematic review, we found 27 studies evaluating the effect of supplemental oxygen therapy and 9 studies evaluating the effect of

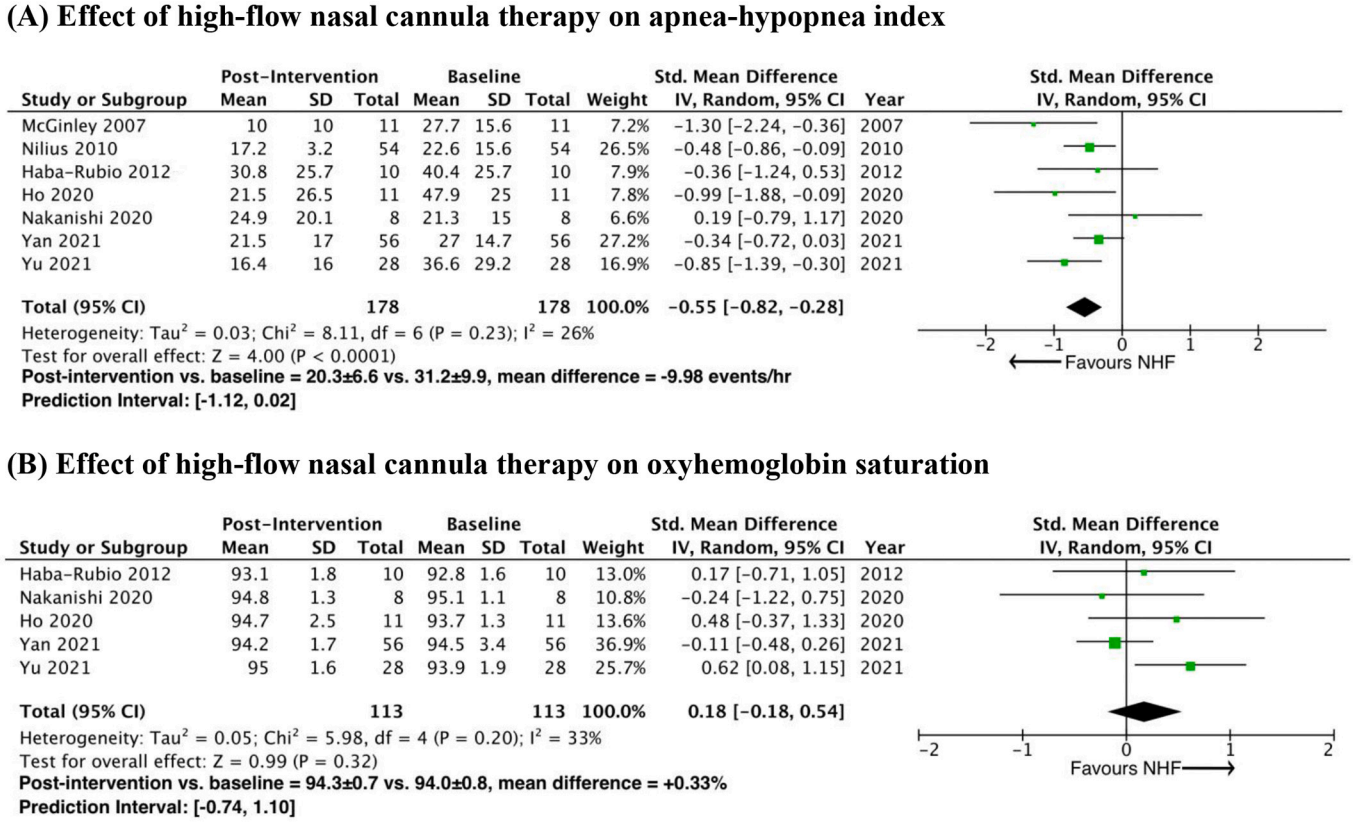

Fig. 4. Effect of high-flow nasal cannula therapy on apnea-hypopnea index and oxyhemoglobin saturation. Fig. 4A. Effect of high-flow nasal cannula therapy on apnea-hypopnea index. Fig. 4B Effect of high-flow nasal cannula therapy on oxyhemoglobin saturation.

Abbreviations: Chi^2, Chi-squared statistic; CI, confidence interval; df, degrees of freedom; I^2, variation attributable to heterogeneity; IV, inverse variance; SD, standard deviation; Std. Mean difference, standardized mean difference; Tau^2, Tau-squared estimate.

HFNC on patients with OSA. Our meta-analysis showed that patients with OSA undergoing oxygen therapy had a significant reduction in AHI by 31% and increase in SpO_2 by 5% versus baseline. Patients with OSA undergoing CPAP also had a significant reduction in AHI by 84% and increase in SpO_2 by 3% versus baseline. When comparing the effectiveness of supplemental oxygen therapy and CPAP, CPAP was 53% more effective in reducing AHI compared to oxygen therapy. However, both CPAP and oxygen therapy demonstrated similar effectiveness in increasing SpO_2. When analyzing studies investigating HFNC therapy in patients with OSA, we found that patients undergoing HFNC therapy had a significant decrease in AHI by 36%, but no change in SpO_2.

CPAP is the primary treatment choice for patients with OSA as it prevents oxygen desaturation, reduces AHI, improves SpO_2, and shortens hospital LOS [3,10,16]. CPAP may be helpful in sleep apnea patients with cardiovascular diseases [8], hypertension [61], and diabetes mellitus [62]. Despite its therapeutic effectiveness, its adherence is low due to mask discomfort, xerostomia, and perceived ineffectiveness [11]. One recent cohort study followed 132 surgical patients diagnosed with OSA with CPAP prescription [63]. Among patients with a preoperative CPAP prescription, approximately 50% were consistently adherent, and 50% percent were CPAP non-adherent. CPAP adherence was associated with improved preoperative ODI, and the benefit was maintained on the first postoperative night after surgery [63]. Surgical patients who were non-adherent to CPAP were three times more likely to require oxygen therapy than those that were CPAP-adherent [63].

In a study of 823 patients with unrecognized OSA undergoing major non-cardiac surgery [64], those requiring postoperative oxygen therapy were mostly male with larger neck circumferences and higher STOP-Bang scores. Those responding to oxygen therapy were likely to have severe OSA and worse preoperative nocturnal hypoxemia [64].

Opioid-induced apneas may manifest as a drop in end-tidal CO_2 and oxygen saturation. Oxygen therapy may mask this, even with end-tidal CO_2 monitoring and leave some patients potentially vulnerable to adverse events. Comorbidities may play an essential role in oxygen therapy and CO_2 retention. Three studies showed a significant overnight increase in CO_2 levels following supplemental oxygen, of which two studies included patient populations with chronic obstructive pulmonary disease (COPD). Specifically, patients with COPD, cystic fibrosis, obesity hypoventilation syndrome, and OSA may have higher baseline CO_2 levels [17,48]. In a RCT study [16], surgical patients with newly diagnosed OSA were randomized to either postoperative oxygen or no oxygen therapy. Eleven percent of surgical patients with OSA who received oxygen therapy in the postoperative setting had significant CO_2 retention despite increased SpO_2, and decreased desaturation events [16]. In this clinical scenario, the ability of pulse oximetry to detect significant desaturations and hypoventilation may be masked during the administration of oxygen therapy [18]. This may result in a delayed response to prolonged hypoventilation, resulting in hypercarbia, CO_2 narcosis, and respiratory failure or cardiopulmonary arrest [65]. The additional risk of respiratory depression in surgical patients with OSA should be considered, as these patients may have heightened sensitivity to anesthetics, sedatives, and opioids [2–5]. These patients may need enhanced postoperative monitoring.

Studies reporting on the clinical and perioperative outcomes of oxygen therapy in medical and surgical settings remain limited. However six studies reported psychological outcomes [28,29,32,35,45,61]. Patients with OSA experience hypoxemia and poor sleep quality, which may be responsible for the pathogenesis of psychological symptoms [66]. These studies reported improved psychological outcomes with oxygen therapy for patients with OSA [28,35,41,45], while two reported no significant improvement [29,32]. One RCT that randomized medical patients into oxygen therapy or CPAP intervention found that both contributed to improved psychological symptoms. However, the oxygen therapy group did not significantly reduce AHI [35]. Improved SpO_2 may be associated with enhanced psychological outcomes [35]. While these studies with small sample sizes reported on psychological outcomes, further robust studies are required to fully understand the clinical effect of oxygen therapy on psychological outcomes [28,35,45,61]. The literature on HFNC therapy for adult patients with OSA is novel and emerging. In pediatric patients with OSA, HFNC effectively reduces AHI and increases SpO_2 nadir [67]. The use of HFNC has also been explored in the surgical setting. In patients who were obese and undergoing induction of anesthesia, HFNC was found to show similar effectiveness in maintaining oxygenation parameters during the apneic phase of induction when compared to supplemental oxygen provided through facemask [68]. Another study exploring surgical patients with OSA found that combined HFNC therapy and upper body elevation was more effective in reducing postoperative respiratory complications than HFNC therapy alone [69].

Due to the small number of studies investigating oxygen therapy and HFNC therapy in surgical patients, our included studies mostly consisted of sleep clinics, cardiology clinics, or stroke unit patients. For the literature in surgical patients, we found only one study on oxygen therapy [16] and one study in HFNC therapy [60]. Evidence on the postoperative clinical outcomes of supplemental oxygen and HFNC therapy is limited. Surgical patients with OSA have an increased risk of perioperative complications, including cardiovascular events, desaturation, reintubation, and admission to the intensive care unit [3–6]. Perioperative control of AHI may prevent exacerbation of post-operative complications in patients with OSA during sleep [10]. Our meta-analysis showed a statistically significant reduction of AHI from 41.4 events/h to 28.6 events/h for oxygen therapy and 31.9 events/h to 20.3 events/h for HFNC therapy. Although these reductions were statistically significant, both therapies could not demonstrate a sufficient clinical decrease in AHI to reduce the severity of OSA to mild OSA. When comparing to the post-operative effectiveness of CPAP in surgical patients with OSA, a mean difference in pre-operative AHI from 37 $\pm$ 19 events/h to a postoperative AHI of 12 $\pm$ 16 events/h was found [10].

Despite the difference in AHI reduction between this review and Nagappa et al. [10], there is a need for CPAP-alternative treatments. In the surgical setting, there may be insufficient time to identify and treat newly diagnosed OSA patients [12]. Non-compliant CPAP patients also need effective alternative therapy options. Patients on HFNC have reported mask discomfort, nasal dryness, and eye irritation [70]. Only two studies analyzed the relative patient compliance of HFNC therapy versus CPAP in patients with OSA, with mixed results [20,60]. Further investigations of CPAP-alternative treatments in surgical settings for patients with OSA are needed to fully understand patient compliance to CPAP-alternative therapies, and their relative clinical effectiveness to CPAP for post-operative management [63].

There are some limitations in this systematic review and meta-analysis. First, there was moderate heterogeneity amongst the included studies due to variability in study design and different clinical settings. Some of the included articles did not have a randomized allocation of treatment groups and were at risk for selection bias. Some studies were crossover designs, which may be at risk for carryover confounding effects when transitioning participants between treatment arms. Another limitation was the diverse patient populations. The varying degree of comorbidities and differences in patient populations may affect the generalizability of the findings and contribute to the heterogeneity. There may also be a risk of reporting bias and incomplete data retrieval at the review level. Future studies should report the distribution of OSA severity within their study sample to enable granular analysis for the clinical effectiveness of OSA interventions. Finally, our search strategy included only English-language publications, which may have introduced bias. Nevertheless, our findings add valuable information and provides the impetus for future studies on surgical patients with OSA during the perioperative period.

5. Conclusion

Our systematic review and meta-analysis demonstrates that oxygen

therapy effectively reduces AHI, but CPAP therapy is more effective in reducing AHI than oxygen therapy. We found that oxygen therapy and CPAP have similar effectiveness in increasing SpO_2 and decreasing CT90. Lastly, HFNC therapy effectively reduced AHI, but did not substantially increase SpO_2. Although oxygen therapy and HFNC therapy effectively reduce AHI, more research on clinical outcomes are needed to draw conclusions.

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