


RESEARCH ARTICLE

In search of a better CPAP interface: A network meta-analysis comparing nasal masks, nasal pillows and oronasal masks

Li-Yang Chen^{1†} | Yung-Hsuan Chen^{2,3†} | Shih-Wen Hu⁴ | Ming-Tzer Lin^{2,5} |
 Pei-Lin Lee^{2,3,6,7}  | Ambrose A. Chiang⁸ | Yu-Kang Tu⁹

¹Department of Internal Medicine, Tainan Sin Lau Hospital, Tainan, Taiwan

²Center of Sleep Disorder, National Taiwan University Hospital, Taipei, Taiwan

³Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

⁴Policy Wisdom, LLC, Miami, Florida, USA

⁵Department of Internal Medicine, Hsiao Chung-Cheng Hospital, New Taipei, Taiwan

⁶School of Medicine, National Taiwan University, Taipei, Taiwan

⁷Center for Electronics Technology Integration, National Taiwan University, Taipei, Taiwan

⁸Division of Sleep Medicine, Louis Stokes VA Medical Center; Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

⁹Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

Correspondence

Pei-Lin Lee, Centre of Sleep Disorder, National Taiwan University Hospital, No. 7, Zhongshan South Road, Taipei 100, Taiwan.
 Email: leepeilin@ntu.edu.tw

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Summary

Until now, no study has directly network meta-analysed the impact of nasal masks, nasal pillows and oronasal masks on continuous positive airway pressure therapy in patients with obstructive sleep apnea. This study aimed to meta-analyse the impact of three kinds of nasal interfaces with both network meta-analysis and pairwise comparison. PubMed, EMBASE, CENTRAL and [ClinicalTrials.gov](https://www.clinicaltrials.gov) were systematically searched from inception to December 2020 for studies that compared the three types of nasal interfaces for treating obstructive sleep apnea with continuous positive airway pressure. The outcomes were residual apnea-hypopnea index, continuous positive airway pressure, and nightly average usage. The network meta-analysis was conducted using multivariate random-effects in a frequentist framework where three interfaces were ranked with the surface under the cumulative ranking probabilities. The pairwise comparison was conducted using random-effects meta-analysis. Twenty-nine articles comprising 6378 participants were included. The pairwise comparison showed both nasal masks and nasal pillows were associated with lower residual apnea-hypopnea index, lower continuous positive airway pressure, and higher continuous positive airway pressure adherence compared with oronasal masks. The surface under the cumulative ranking confirmed that nasal masks were associated with the lowest residual apnea-hypopnea index and highest adherence, while pillows were associated with the lowest continuous positive airway pressure. The meta-regression identified that lower pretreatment apnea-hypopnea index and continuous positive airway pressure determined during continuous positive airway pressure titration (versus determined during continuous positive airway pressure therapy) was associated with lower continuous positive airway pressure with nasal masks and nasal pillows. In conclusion, compared with oronasal masks, nasal masks and nasal pillows are better interfaces, especially in patients with lower pretreatment apnea-hypopnea index and those with the therapeutic pressure determined during continuous positive airway pressure titration.

† Li-Yang Chen and Yung-Hsuan Chen contributed equally to this study.

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KEYWORDS

compliance, positive airway pressure, randomized controlled trial, sleep-disordered breathing, titration

1 | INTRODUCTION

Continuous positive airway pressure (CPAP) is the standard treatment for obstructive sleep apnea (OSA), and has been shown to efficaciously reverse apnea–hypopnea, and improve daytime sleepiness, blood pressure, dyslipidaemia and quality of life (Patil et al., 2019). However, its impact on cardiovascular outcome was only noticed in the observational trials (Lin et al., 2018; Marin, Carrizo, Vicente, & Agusti, 2005) but not in the large-scale randomized controlled trials (RCTs; Barbe et al., 2012; McEvoy et al., 2016; Peker et al., 2016). Two RCTs showed a significant cardiovascular risk reduction in patients who used CPAP ≥ 4 hr per night than those used < 4 hr per night (Barbe et al., 2012; Peker et al., 2016), while the association was not observed in other RCTs (McEvoy et al., 2016). The effectiveness of CPAP treatment is determined by both the therapeutic efficacy measured by the reduction of apnea–hypopnea index (AHI) and the CPAP adherence (Sutherland, Phillips, & Cistulli, 2015). Studies suggested that CPAP usage ≥ 4 hr per night and ≥ 6 hr per night are required for lowering blood pressure and improving daytime function, respectively (Fava et al., 2014; Weaver et al., 2007). Initial nasal interface fitting and CPAP adherence monitoring are crucial in improving CPAP adherence (R. G. Andrade et al., 2014; Bachour, Vitikainen, Virkkula, & Maasilta, 2013; Borel et al., 2013; Chai, Pathinathan, & Smith, 2006).

Nasal masks, nasal pillows and oronasal masks are the three commonly used nasal interfaces. Nasal masks and nasal pillows allow delivery of positive airway pressure through the nose, while oronasal masks allow airflow through both the nasal and oral routes. Overall, nasal masks work for the majority of patients. Alternatively, oronasal masks are options for patients with nasal obstruction or substantial oral leaks (Beecroft, Zanon, Lukic, & Hanly, 2003; Lebret et al., 2015; Lebret et al., 2018; Prosis & Berry, 1994). For those who have claustrophobia, mask-induced nose bridge pressure sores, thick facial hairs, or frequent mask dislodgement due to tossing and turning in sleep, nasal pillows provide another suitable option. Previous studies suggested that nasal pillows have equal efficacy and objective adherence as nasal masks (Bachour et al., 2013; Borel et al., 2013; Ebben, Oyegbile, & Pollak, 2012; Lanza et al., 2018; Massie & Hart, 2003; Ryan, Garvey, Swan, Behan, & McNicholas, 2011; Zhu, Wimms, & Benjafield, 2013).

Several studies have compared the effects of different interfaces on outcomes including residual AHI, CPAP pressure, and adherence. Yet, the results remain inconsistent (Bachour et al., 2013; Bakker, Neill, & Campbell, 2012; Beecroft et al., 2003; Bettinzoli et al., 2014; Blanco, Ernst, Salvado, & Borsini, 2019; Borel et al., 2013; Casanova et al., 2013; Deshpande et al., 2016; Duarte, Mendes, Oliveira, Magalhaes-da-Silveira, & Gozal, 2020; Ebben, Milrad, Dyke, Phillips, & Krieger, 2016; Ebben, Narizhnaya, Segal, Barone, & Krieger, 2014;

Ebben et al., 2012; Foellner et al., 2020; Goh et al., 2019; Kaminska et al., 2014; Lanza et al., 2018; Lebret et al., 2015; Lebret et al., 2018; Massie & Hart, 2003; Mortimore, Whittle, & Douglas, 1998; Prosis & Berry, 1994; Rowland et al., 2018; Ryan et al., 2011; Schell & Soose, 2017; Shirlaw, Duce, Milosavljevic, Hanssen, & Hukins, 2019; Teo et al., 2011; Westhoff & Litterst, 2015; Zampogna et al., 2019; Zhu et al., 2013) as RCTs are commonly underpowered by small sample sizes, while large-scale observational studies may be biased due to various confounders derived from participant characteristics and study design. A Cochrane systematic review (Chai et al., 2006) previously concluded that the optimal form of CPAP delivery interface remained unclear. A more recent random-effects meta-analysis comparing the nasal masks and oronasal masks (R. G. S. Andrade et al., 2018) suggested that nasal masks were associated with better efficacy in lowering AHI, better adherence, and lower CPAP setting than oronasal masks. Since this meta-analysis, more studies have compared the effects of different interfaces (Blanco et al., 2019; Duarte et al., 2020; Foellner et al., 2020; Goh et al., 2019; Lanza et al., 2018; Lebret et al., 2018; Rowland et al., 2018; Schell & Soose, 2017; Shirlaw et al., 2019; Zampogna et al., 2019). A recent systemic review for positive airway pressure treatment of adult OSA suggested that although the residual AHI was higher in oronasal interfaces than nasal interfaces, this difference may not be clinically significant (Patil et al., 2019).

Network meta-analysis (NMA) has the capability to synthesize and compare both direct and indirect evidence from multiple clinical trials as randomized trials can rarely compare all available therapeutic options. NMA is especially useful when direct evidence is scarce or unavailable. In the case of CPAP mask comparison, oronasal masks and nasal pillows are often compared with nasal masks, but are seldom compared with each other. This study aimed to perform both NMA and pairwise meta-analyses to compare the impact of nasal pillows, nasal masks and oronasal masks on residual AHI, CPAP pressure, and adherence in patients with OSA. We also performed subgroup analysis and meta-regression to identify if the mask performance may be associated with patient characteristics such as pretreatment AHI level, CPAP-naïvety (versus CPAP-experienced), or outcomes determined during CPAP titration (versus determined during home CPAP therapy).

2 | METHODS

2.1 | Data source and search strategy

A systematic search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Hutton et al., 2015). The present meta-analysis was

registered with the International Prospective Register for Systematic Reviews (CRD42018114447). The literature search, eligibility assessment, quality and risk of bias assessment, and data extraction were conducted by SWH, LYC and YHC independently, while any discrepancies were resolved through PLL. A systematic search of PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and [ClinicalTrials.gov](https://www.clinicaltrials.gov) from their inception to 31 December 2020, using relevant text words and medical subject heading (MeSH) terms related to sleep apnea, CPAP and mask (Table S1), was performed. There were no time frame or language restrictions. The [ClinicalTrials.gov](https://www.clinicaltrials.gov) website was also searched for trials registered but not yet published. The references listed in the included reports were manually scanned for relevant reports.

2.2 | Screening of articles and inclusion criteria

After removing duplicates, the titles and abstracts of the retrieved studies were reviewed to select those eligible for full-text review. Studies comparing the interfaces in patients with OSA, defined with AHI, respiratory disturbance index or oxygen desaturation index, were considered eligible. We excluded studies on paediatric patients (age < 18 years), without CPAP interventions, and studies without the comparison of interfaces. We also sequentially excluded non-original studies (including case reports, case series, reviews, meta-analyses or conference abstracts without further publication) and studies without the outcomes of interest.

2.3 | Quality assessment

The risk of bias was assessed using Cochrane Collaboration's tool for RCTs (J. P. Higgins et al., 2011), with each being classified as low, high or unclear. For observational studies, the risk of bias was evaluated according to Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I; J. A. Sterne et al., 2016), with each being classified as mild, moderate, serious or critical (Supplementary Methods).

2.4 | Data extraction

The data including the name of the author, year of publication, sample size, study design, mask type and manufacturer, participant characteristics (age, gender, body mass index), pretreatment AHI, CPAP treatment before participant enrollment, the timing of outcome determination, follow-up duration, residual AHI, CPAP pressure, and adherence were extracted. For studies without the required information, we made attempts to contact the authors for additional details.

2.5 | Pairwise comparison

The outcomes were residual AHI, CPAP pressure, and adherence measured according to the nightly use of CPAP in hours. Pairwise

comparisons of mean and standard deviation (SD) were analysed. If the data were reported as the median and interquartile range (IQR), the median was used to estimate the mean difference, while the IQR was divided by 1.35 to estimate the standard deviation (J. P. T. Higgins & Deeks, 2011). The pooled effect of differences in outcomes was calculated using random-effect generic inverse variance (J. P. Higgins, Thompson, Deeks, & Altman, 2003). Results were presented using mean difference (MD) with 95% confidence interval (CI), and were illustrated with the Forest plot.

Publication bias was assessed using Egger's test and visualized with funnel plots using MD with a standard error. Outcomes reported in fewer than 10 studies were not tested with Egger's test due to the lack of power to detect real asymmetry (J. A. C. Sterne, Egger, & Moher, 2011).

Heterogeneity across studies was assessed using the χ^2 -test and I^2 statistics. A Cochran Q with a p -value < 0.1 was considered to indicate heterogeneity, while the I^2 statistic was used to indicate low (0%–25%), moderate (26%–75%) and significant (76%–100%) heterogeneity. To explore heterogeneity, subgroup analyses were performed by grouping reports including trial design (RCT versus non-RCT), CPAP experience before enrollment (CPAP-naïve versus CPAP-experienced), and the timing of CPAP pressure determination (during titration versus during CPAP therapy at home). The direct pairwise meta-analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and R 3.5.3 (R Development Core Team) with the metaphor package.

2.6 | Network meta-analysis

Frequentist NMA was implemented using the suite “network” for the statistical software STATA (version 17.0). Random-effects models were utilized for all the analyses to account for the expected clinical and methodological heterogeneity. In the network diagram, each interface is represented by a node, and the comparisons between interfaces are represented by the edges between the nodes. The size of the nodes is proportional to the number of subjects receiving the intervention, and the width of the edge is proportional to the number of trials that compare the two interventions. The ranking of treatments was presented by the surface under the cumulative ranking curve (SUCRA), ranging from 0 to 1. SUCRA is interpreted as the performance of an intervention compared with a hypothetical perfect intervention. The greater the SUCRA value, the better the performance of an intervention is. We applied the design-by-treatment interaction model to assess the overall inconsistency within the NMA, and used the loop inconsistency model and side-splitting model to evaluate the consistency between the direct and indirect evidence for any treatment comparison. Additionally, we assessed the quality of evidence contributing to each network estimate using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (Salanti, Del Giovane, Chaimani, Caldwell, & Higgins, 2014).

Meta-regression was also conducted in both pairwise standard meta-analysis and NMA to investigate the associations between

parameters (pretreatment AHI, CPAP-naïve versus CPAP-experienced patients, and pressure determined during CPAP titration versus home CPAP therapy) and outcomes to identify sources of heterogeneity.

3 | RESULTS

3.1 | Search results and included studies

The systematic literature search identified 7136 articles, of which 44 articles were reviewed for the full text. Among them, 29 articles (28 were in English and one was in French) comprising 6378 participants were included for the meta-analysis (Figure 1; Table 1; Supplementary Results; Bachour et al., 2013; Bakker et al., 2012; Beecroft et al., 2003; Bettinzoli et al., 2014; Blanco et al., 2019; Borel et al., 2013; Casanova et al., 2013; Deshpande et al., 2016; Duarte et al., 2020; Ebben et al., 2016; Ebben et al., 2014; Ebben et al., 2012; Foellner et al., 2020; Goh et al., 2019; Kaminska et al., 2014; Lanza et al., 2018; Lebret et al., 2015; Lebret et al., 2018; Massie & Hart, 2003; Mortimore et al., 1998; Prorise & Berry, 1994; Rowland

et al., 2018; Ryan et al., 2011; Schell & Soose, 2017; Shirlaw et al., 2019; Teo et al., 2011; Westhoff & Litterst, 2015; Zampogna et al., 2019; Zhu et al., 2013). The characteristics of these studies are listed in Table 1. The article by Mortimore et al. (1998) included both an RCT and an observational portion, and we reported them separately in Table 1. Among 18 observational studies, 14 included two or three groups of participants each for one specific interface (Bachour et al., 2013; Beecroft et al., 2003; Bettinzoli et al., 2014; Blanco et al., 2019; Borel et al., 2013; Casanova et al., 2013; Deshpande et al., 2016; Duarte et al., 2020; Ebben et al., 2016; Lanza et al., 2018; Lebret et al., 2015; Lebret et al., 2018; Schell & Soose, 2017; Zampogna et al., 2019), and four studied different interfaces in one group of subjects (Kaminska et al., 2014; Mortimore et al., 1998; Prorise & Berry, 1994; Westhoff & Litterst, 2015). The number of studies and participants comparing all interfaces on three primary outcomes are illustrated in Figure 2.

Most of the enrolled participants were obese, male, and had a high pretreatment AHI (Table S2a). The timing of outcomes measured was listed in Table S2b. The titration duration ranged from 1 to 5 days, and the CPAP therapy duration ranged from 4 to a mean of 696 days. The information on products and manufacturers of masks is provided in the 20 studies (Table S2c), of which ResMed, Philips-Respironics, and Fisher & Paykel are the top three most common. In nine studies, masks used were from more than one manufacturer, while masks were from the same manufacturer in 11 studies.

3.2 | Bias assessment

Twelve RCTs were examined, and five of these studies properly described the procedure of randomization and allocation concealment (Bakker et al., 2012; Ebben et al., 2014; Goh et al., 2019; Rowland et al., 2018; Shirlaw et al., 2019). The data analysts were blinded in four studies (Bakker et al., 2012; Ebben et al., 2014; Goh et al., 2019; Rowland et al., 2018; Figure S1).

The 18 non-RCTs were assessed using ROBINS-I, and all were qualified for meta-analysis (Table S3). Two studies (Kaminska et al., 2014; Westhoff & Litterst, 2015) had a critical bias in the selection of the participants as both studies recruited participants whose respiratory events were inadequately controlled with oronasal masks and were subsequently treated with nasal masks. The funnel plots and Egger's tests for pairwise comparisons were presented in Figure 3. There was no publication bias except for one study comparing nasal masks and nasal pillows on CPAP pressure showing positive Egger's test ($p = 0.022$). According to GRADE (Table S4), the quality of evidence was low to very low for all the comparison results in three outcomes as non-RCTs formed most of the evidence.

3.3 | Pairwise comparison outcomes

For residual AHI (Figure 4), nasal masks (-3.58 per hr, 95% CI -5.03 to -2.14 , high heterogeneity) and nasal pillows (-3.03 per hr, 95% CI



FIGURE 1 Flow diagram of our literature search strategy

TABLE 1 Study characteristics (a) and outcome (b) of 30 studies included

Author (year)	Design	CPAP-naïve	Total mask no.	Nasal mask no.	Oronasal mask no.	Pillow no.	Age, mean (SD), years	Male, no. (%)	BMI, mean (SD), kg m ⁻²	Pretreatment AHI, mean (SD), events per hr	Outcome measured
Prosise (1994)	O	No	5	5	5	0	60.0 (14.6)	NA	NA	62.3 (28.2)	Titration
Mortimore (1998-1)	R	Yes	20	20	20	0	52.0 (13.4)	NA	32.0 (4.5)	34.0 (23.3)	Therapy
Mortimore (1998-2)	O	No	10	10	10	0	50.0 (9.5)	NA	31.0 (12.6)	46.0 (31.6)	Therapy
Beecroft (2003)	O	Yes	72	65	7	0	50.6 (11.7)	50 (70)	32.5 (9.0)	40.6 (25.8)	Titration, therapy
Massie (2003)	R	Yes	39	39	0	39	48.7 (8.5)	32 (82)	35.9 (6.4)	47.1 (35.1)	Titration, therapy
Ryan (2011)	R	Yes	21	21	0	21	49.0 (10.0)	19 (90)	35.4 (7.6)	52.4 (21.6)	Therapy
Teo (2011)	R	Yes	24	24	24	0	51.3 (13.3)	18 (75)	33.8 (9.4)	47.0 (15.2)	Titration
Bakker (2012)	R	No	12	24	24	0	48.8 (NA)	11 (92)	37.7 (5.0)	59.8 (28.6)	Therapy
Ebben (2012)	R	Yes	55	21	16	18	55.6 (14.4)	33 (60)	33.2 (7.3)	36.3 (22.0)	Titration
Bachour (2013)	O	No	709	577	66	66	58.0 (12.0)	569 (78)	NA	NA	Therapy
Borel (2013)	O	Yes	2311	1443	605	263	57.3 (12.2)	1641 (71)	32.2 (6.6)	40.7 (20.6)	Therapy
Casanova (2013)	O	No	605	309	296	0	60.5 (12.5)	445 (74)	NA	41.7 (19.4)	Therapy
Zhu (2013)	R	No	20	20	0	20	64.6 (9.5)	15 (75)	NA	NA	Therapy
Bettinzoli (2014)	O	No	109	67	42	0	58.3 (12.9)	170 (78)	33.9 (6.3)	41.1 (20.5)	Titration
Ebben (2014)	R	Yes	14	14	14	0	62.0 (15.0)	11 (79)	29.6 (6.0)	36.5 (14.5)	Therapy
Kaminska (2014)	O	No	6	6	6	0	53.5 (11.9)	5 (83)	28.1 (4.9)	56.8 (40.1)	Titration
Lebret (2015)	O	No	34	27	7	0	57.5 (6.7) ^e	22 (65)	32.6 (4.5) ^e	45 (8.9) ^e	Therapy
Westhoff (2015)	O	No	54	54	54	0	64.4 (12.8)	61 (94)	32.2 (8.1)	31.8 (16.3)	Titration
Deshpande (2016)	O	Yes	358	124	165	69	57.7 (14.1)	226 (63)	34.1 (7.9)	41.9 (31.1)	Titration
Ebben (2016)	O	No	10 ^a	5	4	0	59.1 (11.1)	8 (89)	30.4 (6.4)	46.0 (27.8)	Therapy
Schell (2017)	O	Mixed	218	88	75	55	53.0 (12.6)	163 (75)	34.1 (7.3)	32.4 (28.7)	Therapy
Goh (2018)	R	Yes	85	85	85	85	46.0 (12.0)	71 (84)	29.9 (5.6)	53.6 (24.0)	Therapy
Lanza (2018)	O	Yes	144	42	0	102	58.1 (12.9)	110 (76)	33.9 (7.6)	44.5 (NA)	Titration, therapy
Lebret (2018)	O	Yes	74 ^b	58	14	0	55.8 (13.0) ^e	51 (65)	32.9 (6.7) ^e	44.3 (26.6) ^e	Therapy
Rowland (2018)	R	Yes	48 ^c	37	39	0	56.6 (1.8)	32 (68)	35.3 (1.1)	57.6 (3.6)	Therapy
Shirlaw (2018)	R	No	60	60	60	0	64.0 (10.0)	45 (75)	34.5 (6.7) ^e	32.0 (18.8) ^e	Therapy

(Continues)

TABLE 1 (Continued)

(a)												
Author (year)	Design	CPAP-naïve	Total no.	Nasal mask no.	Oronasal mask no.	Pillow no.	Age, mean (SD), years	Male, no. (%)	BMI, mean (SD), kg m ⁻²	Pretreatment AHI, mean (SD), events per hr	Outcome measured	
Bianco (2019)	O	Yes	707	532	71	104	59.1 (12.2)	513 (73)	34.1 (6.7)	33.0	Titration	
Zampogna (2019)	O	Yes	147 ^d	68	45	0	59.0 (4.7) ^e	125 (85)	31 (2.3) ^e	40.0 (9.7) ^e	Therapy	
Duarte (2020)	O	Yes	436	283	153	0	56.0 (14.8) ^e	287 (66)	29.5 (4.9) ^e	NA	Titration	
Foellner (2020)	R	No	29	29	29	0	59.5 (NA)	17 (59)	33.1 (NA)	NA	Titration	
(b)												
Residual AHI, mean (SD), events per hr												
Author (year)	Nasal		Oronasal		Pillow		CPAP pressure, mean (SD), cmH ₂ O			Adherence, mean (SD), hr per night		
	Nasal	Oronasal	Nasal	Oronasal	Nasal	Oronasal	Nasal	Oronasal	Pillow	Nasal	Oronasal	Pillow
Prosise (1994)	7.2 (3.5)	7.6 (4.9)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mortimore (1998-1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.3 (1.8)	4.3 (2.2)	NA
Mortimore (1998-2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.1 (2.2)	4.0 (2.5)	NA
Beecroft (2003)	6.7 (13.3)	9.8 (12.8)	NA	NA	7.7 (2.1)	9.7 (3.2)	NA	NA	NA	5.0 (2.1)	4.5 (1.9)	NA
Massie (2003)	7.0 (7.7)	NA	10.2 (9.8)	NA	8.4 (2.0)	NA	NA	8.9 (2.4)	NA	5.4 (1.6)	NA	5.6 (1.3)
Ryan (2011)	2.6 (2.7)	NA	3.0 (2.9)	NA	NA	NA	NA	NA	NA	5.1 (1.9)	NA	5.0 (1.7)
Teo (2011)	5.3 (3.4)	11.0 (10.4)	NA	NA	12.2 (2.2)	11.9 (1.4)	NA	NA	NA	NA	NA	NA
Bakker (2012) ^f	0.6 (1.2)	2.2 (2.6)	NA	NA	11.0 (2.1)	10.8 (1.7)	NA	NA	NA	6.7 (1.0)	6.4 (1.9)	NA
Ebben (2012)	2.7 (2.3)	3.6 (3.2)	2.8 (2.1)	NA	7.6 (1.5)	10.4 (3.6)	NA	8.8 (3.1)	NA	NA	NA	NA
Bachour (2013)	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.8 (2.8)	4.7 (2.8)	4.7 (3.2)
Borel (2013)	NA	NA	NA	NA	8.9 (2.7)	9.6 (2.5)	NA	8.2 (2.4)	NA	5.5 (3.4)	5.0 (2.7)	5.3 (2.3)
Casanova (2013)	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.6 (2.0)	5.0 (2.2)	NA
Zhu (2013)	1.7 (1.1)	NA	1.9 (1.3)	NA	13.9 (1.9)	NA	NA	13.5 (1.4)	NA	7.2 (1.4)	NA	7.4 (1.4)
Bettinzoli (2014)	2.6 (2.5)	4.5 (4.0)	NA	NA	10.0 (2.0)	11.2 (2.1)	NA	NA	NA	NA	NA	NA
Ebben (2014)	2.9 (2.3)	7.9 (7.0)	NA	NA	7.4 (2.4)	9.3 (4.2)	NA	NA	NA	5.2 (1.7)	4.6 (2.2)	NA
Kaminska (2014)	NA	NA	NA	NA	10.4 (3.0)	16.3 (5.4)	NA	NA	NA	NA	NA	NA
Lebret (2015)	NA	NA	NA	NA	NA	NA	NA	NA	NA	6.4 (2.2) ^e	6.2 (3.1) ^e	NA
Westhoff (2015)	6.0 (3.6)	31.8 (16.3)	NA	NA	7.2 (1.9)	9.5 (2.3)	NA	NA	NA	NA	NA	NA
Deshpande (2016)	6.4 (6.7)	11.3 (11.7)	6.7 (8.5)	NA	10 (3.0)	12.0 (4.1)	NA	11.0 (3.3)	NA	NA	NA	NA
Ebben (2016)	2.5 (2.2)	0.8 (0.9)	NA	NA	9.4 (4.0)	6.8 (1.5)	NA	NA	NA	NA	NA	NA

TABLE 1 (Continued)

Author (year)	Residual AHI, mean (SD), events per hr			CPAP pressure, mean (SD), cmH ₂ O			Adherence, mean (SD), hr per night		
	Nasal	Oronasal	Pillow	Nasal	Oronasal	Pillow	Nasal	Oronasal	Pillow
Schell (2017)	NA	NA	NA	12.4 (4.2)	15.2 (4.1)	12.3 (4.1)	NA	NA	NA
Goh (2018)	4.0 (4.2)	7.2 (5.2)	4.1 (3.3)	8.2 (2.2)	7.7 (2.6)	7.5 (2.0)	4.0 (2.3)	3.3 (2.2)	3.5 (2.2)
Lanza (2018)	1.1 (7.0)	NA	0.7 (6.7)	11.6 (1.6)	NA	11.4 (1.5)	5.3 (1.6)	NA	5.5 (1.8)
Lebret (2018)	10.3 (9.0) ^e	17.5 (10.0) ^e	NA	8.5 (2.6)	8.9 (2.8)	NA	NA	NA	NA
Rowland (2018)	4.0 (3.1)	7.1 (7.7)	NA	NA	NA	NA	5.7 (2.6)	5.5 (2.4)	NA
Shirlaw (2018)	4.9 (4.1) ^e	5.3 (3.3) ^e	NA	11.5 (1.3) ^e	11.7 (1.6) ^e	NA	7.3 (1.6) ^e	7.3 (1.7) ^e	NA
Bianco (2019)	4.6 (4.1)	7.6 (5.2)	3.7 (2.9)	8.3 (2.1)	9.3 (2.6)	7.1 (1.9)	6.3 (1.2)	6.1 (1.1)	6.2 (1.1)
Zampogna (2019)	6.0 (4.4)	6.0 (4.8)	NA	10.7 (1.6)	10.6 (1.6)	NA	4.3 (2.7)	4.3 (2.7)	NA
Duarte (2020)	2.2 (2.5) ^e	4.9 (5.8) ^e	NA	10.7 (2.3) ^e	12.9 (3.3) ^e	NA	NA	NA	NA
Foellner (2020)	2.6 (2.3)	8.5 (6.7)	NA	NA	NA	NA	NA	NA	NA

AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; NA, not available; O, observational; R, randomized controlled trial.

^aOne patient with two unspecified pressure levels was excluded.

^bMask type from two patients was missing.

^cForty-eight patients were randomized into the study. The characteristics at baseline were obtained from 34 completed data.

^dData on the use of masks were available in 113 out of 147 patients.

^eMean and SD were estimated using median and IQR/1.35.

^fBoth APAP and CPAP data were grouped together.

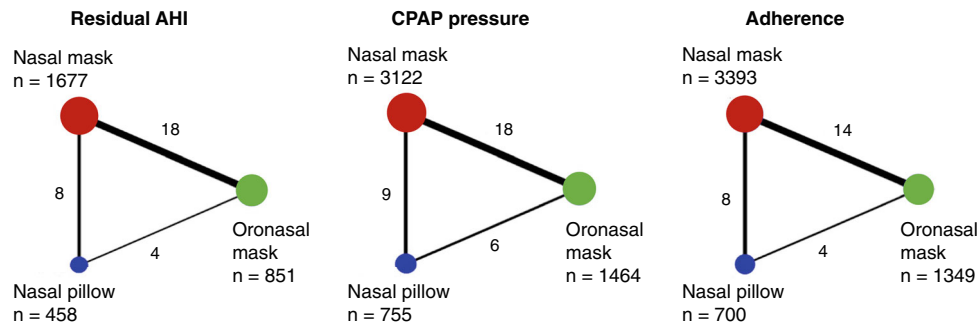


FIGURE 2 Network graph of interface comparison for residual apnea-hypopnea index (AHI), continuous positive airway pressure (CPAP) pressure and CPAP adherence. The number next to each node indicates the number of participants, and the size of each node reflects the proportion of participants. The number next to each edge indicates the number of studies and the edge thickness is proportional to the number of studies

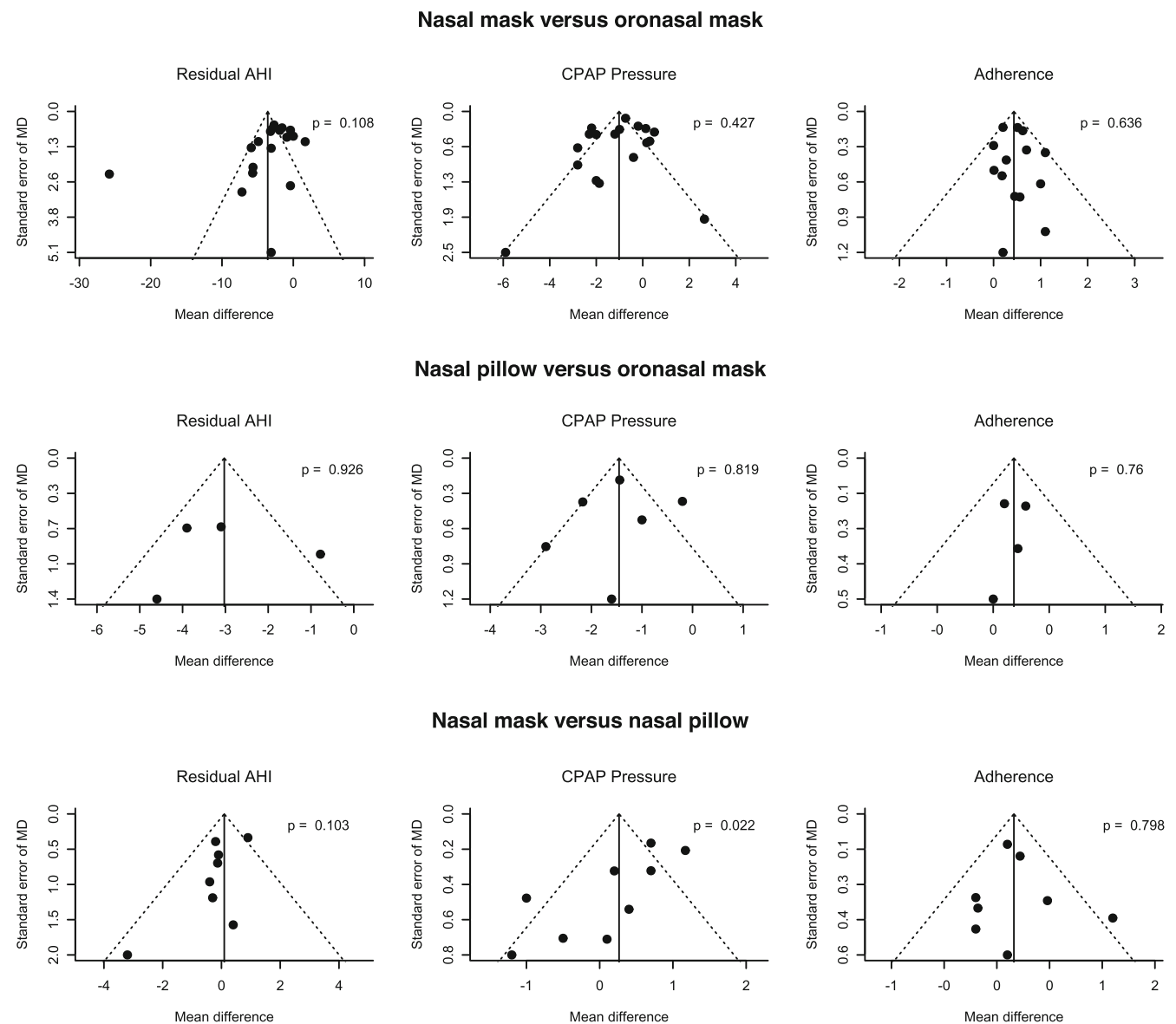


FIGURE 3 Funnel plot of included studies

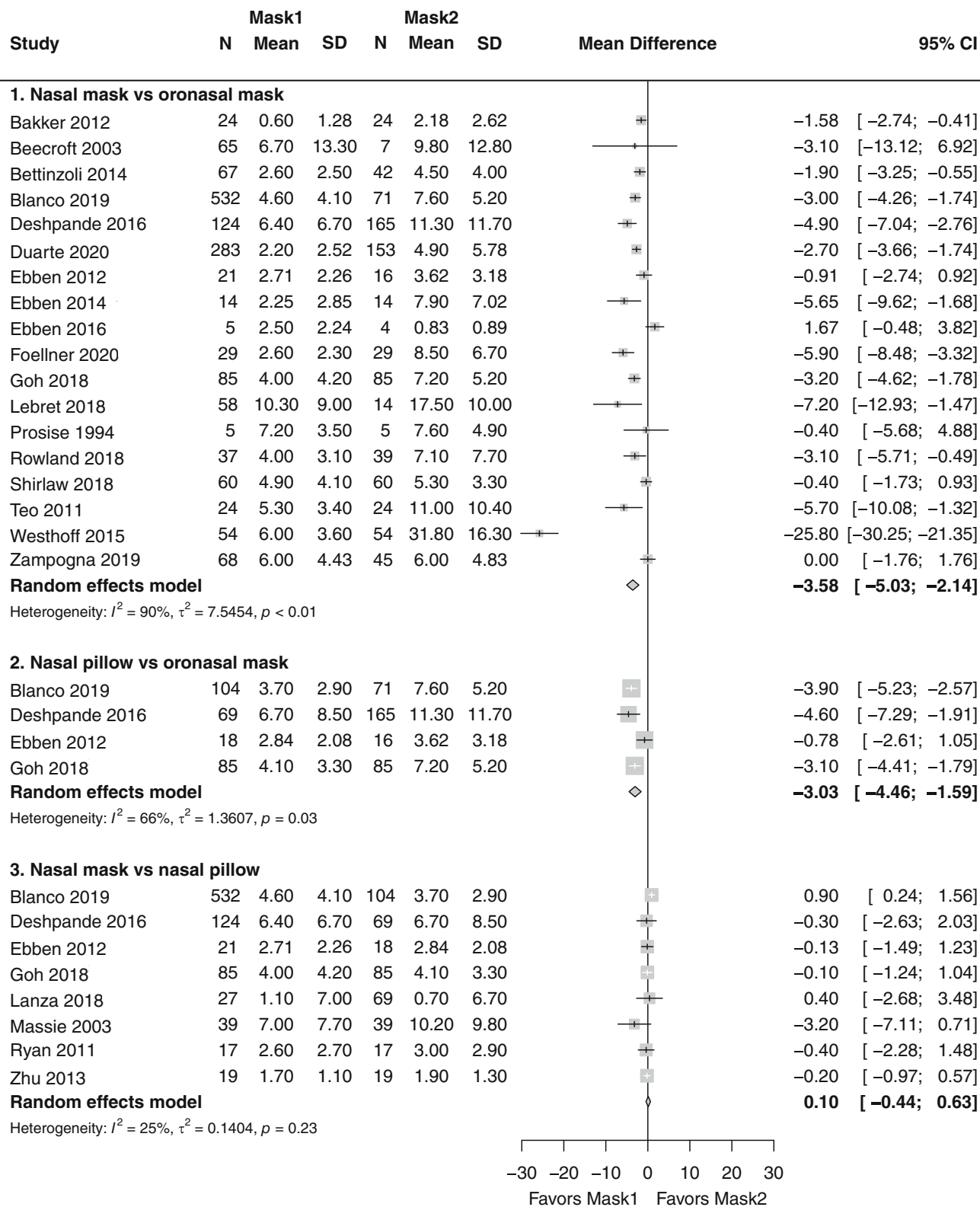


FIGURE 4 Pairwise comparison of different interfaces for residual apnea-hypopnea index (AHI)

-4.46 to -1.59, moderate heterogeneity) were associated with a lower residual AHI compared with oronasal masks, while there was no difference between nasal masks and nasal pillows.

For CPAP pressure (Figure 5), nasal masks (-1.02 cmH₂O, 95% CI -1.51 to -0.53, high heterogeneity) and nasal pillows (-1.45 cmH₂O, 95% CI -2.15 to -0.76, high heterogeneity) were associated with a

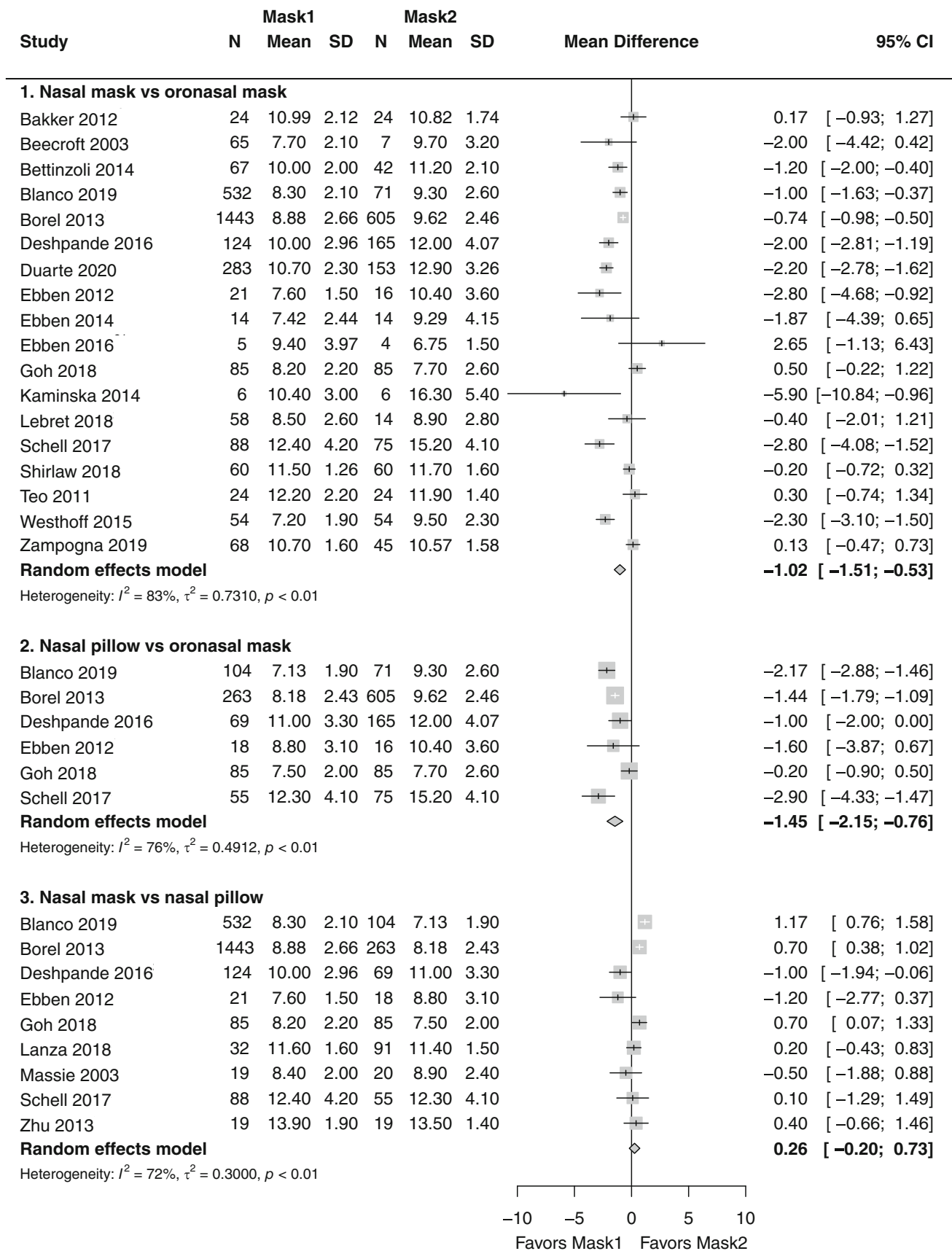


FIGURE 5 Pairwise comparison of different interfaces for continuous positive airway pressure (CPAP) pressure

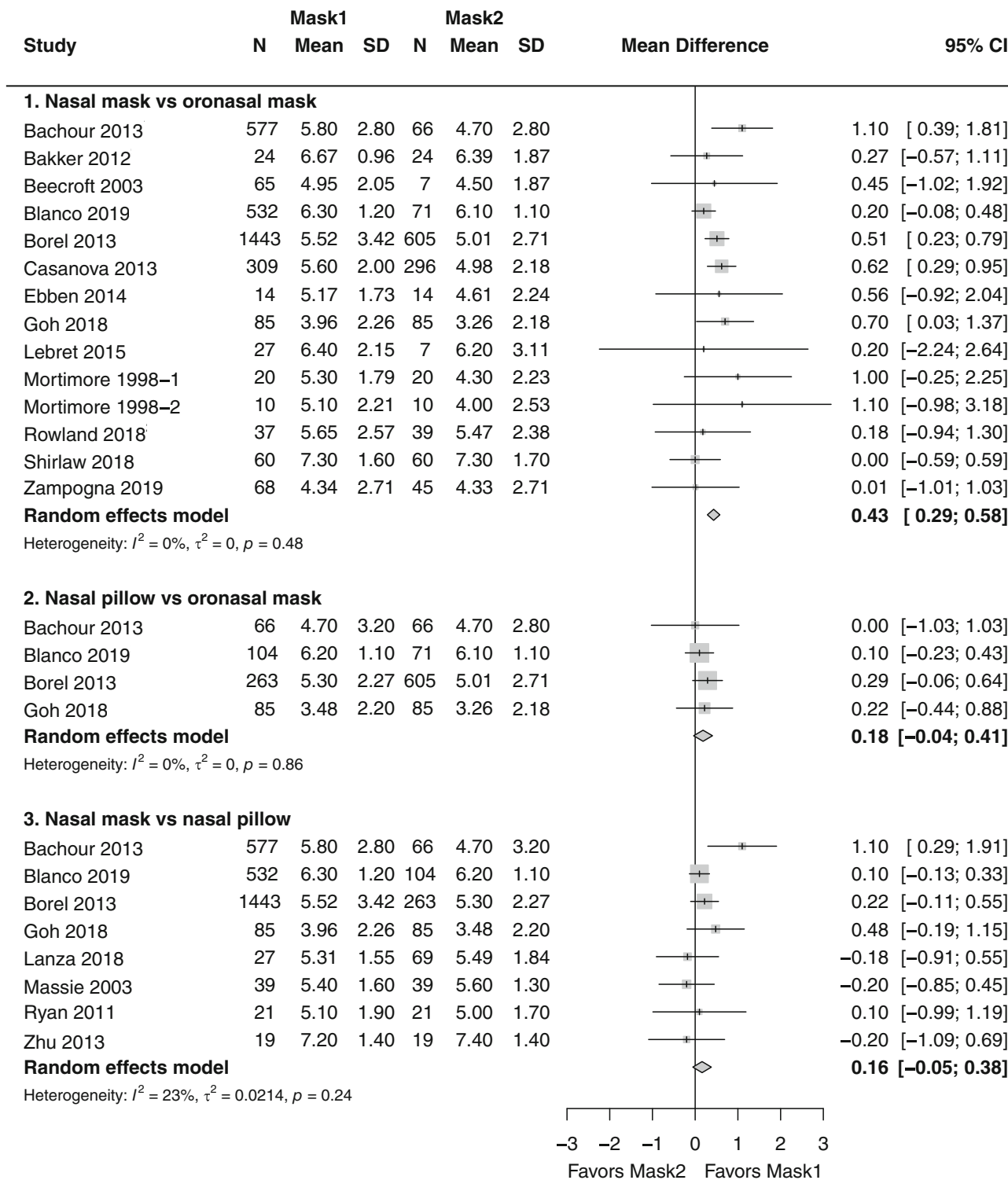


FIGURE 6 Pairwise comparison of different interfaces for CPAP adherence

lower CPAP pressure compared with oronasal masks. There was no difference between nasal masks and nasal pillows.

For CPAP adherence (Figure 6), nasal masks (0.43 hr per night, 95% CI 0.29-0.58, low heterogeneity) and nasal pillows (0.18 hr per night, 95% CI -0.04 to 0.41, low heterogeneity) were associated with a higher adherence compared with oronasal masks. Nasal masks and nasal pillows had similar adherence.

3.4 | NMA outcomes

Nasal masks were associated with the lower residual AHI (-3.88 per hr, 95% CI -5.98 to -1.78), lower CPAP pressure (-1.04 cmH₂O, 95% CI -1.54 to -0.55) and higher adherence (0.43 hr per night, 95% CI 0.25-0.60) compared with oronasal masks. Nasal pillows were associated with lower residual AHI (-3.35 per hr, 95% CI -6.57 to

		Nasal mask	Oronasal mask	Nasal pillow
Residual AHI	Ranking	1	3	2
	SUCRA	81.4	1.2	67.4
CPAP pressure	Ranking	2	3	1
	SUCRA	61.0	0.1	88.9
Adherence	Ranking	1	3	2
	SUCRA	97.3	0.2	52.4

TABLE 2 Cumulative ranking probabilities and SUCRA from NMA

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; SUCRA, surface under the cumulative ranking.

–0.14), lower CPAP pressure (–1.29 cmH₂O, 95% CI –1.97 to –0.60) and higher CPAP adherence (0.26 hr per night, 95% CI 0.04–0.49) compared with oronasal masks. There were no differences between nasal masks and nasal pillows. Nasal masks were best ranked in terms of low residual AHI and better CPAP adherence based on SUCRA (81.4% and 97.3%, respectively), while nasal pillows were ranked best in terms of low CPAP pressure (SUCRA 88.9%; Table 2). We found no evidence of inconsistency between direct and indirect evidence within our NMAs.

3.5 | Subgroup analysis

In the subgroup analysis of RCTs and non-RCTs (Figures S2–S4), the association of nasal masks and nasal pillows with lower pressure compared with oronasal masks was only observed in non-RCTs (Figures S2b and S3b). The nasal pillows were also associated with lower AHI compared with nasal masks in non-RCTs (Figure S4a).

In the subgroup analysis for CPAP-naïve versus CPAP-experienced participants, none of the three primary outcomes was associated with prior CPAP treatment (Figures S5, S6 and S7).

The subgroup analysis of outcomes measured during CPAP titration versus during CPAP therapy at home was performed except the outcome of CPAP adherence (Figures S8–S10). There was only one study (Blanco et al., 2019) that collected the data of CPAP adherence from the titration protocol, and its mean duration was only 3.2 days. It was inappropriate to evaluate the adherence in such a short duration. The subgroup effects were found on the residual AHI and the CPAP pressure. Nasal masks were associated with lower residual AHI and lower pressure measured during CPAP titration compared with oronasal masks (Figure S8a and b).

3.6 | Meta-regression

Mixed-effects meta-regression was performed for one-tenth pretreatment AHI (AHI/10), CPAP treatment before enrollment, and timing of the outcome determined on both pairwise comparisons (Table S5) or NMA (Table S6). In the comparison of nasal masks versus oronasal masks, nasal masks were associated with lower CPAP pressure in the subgroup of CPAP pressure determined at CPAP titration (pairwise:

coefficient –1.255, 95% CI –2.393 to –0.016; Table S5a; NMA: coefficient –1.239, 95% CI –2.123 to –0.354; Table S6). The pretreatment AHI/10 was associated with differences in CPAP pressure between nasal pillows and oronasal masks (pairwise: coefficient 1.015, 95% CI 0.662–1.368; Table S5b; NMA: coefficient 0.009, 95% CI 0.001–0.018; Table S6), which indicates at a lower pretreatment AHI and nasal pillows were associated with much lower CPAP pressure than oronasal masks (Figure 7).

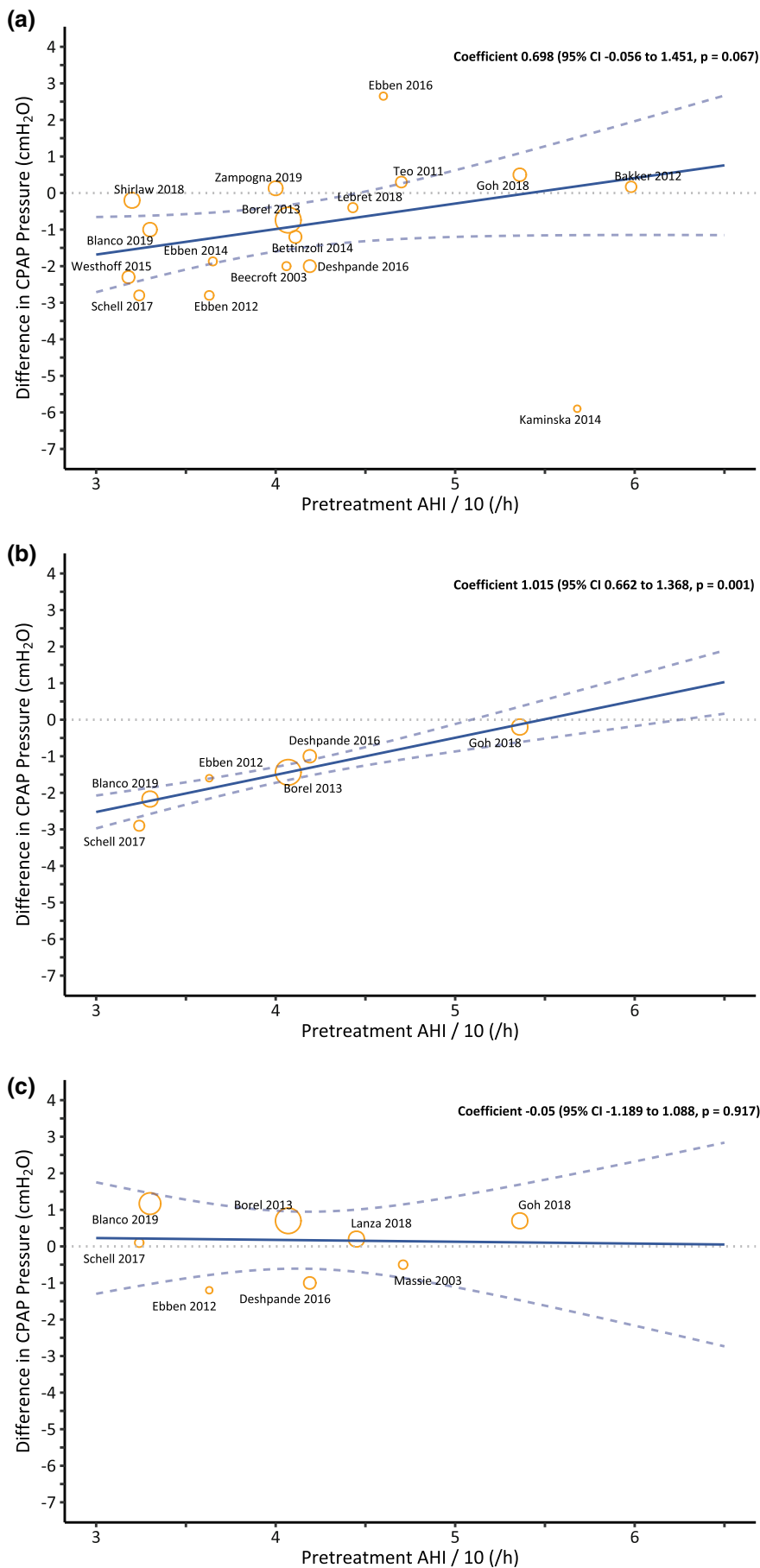
4 | DISCUSSION

In this NMA study, we updated the literature search and compared three interfaces using both NMA and pairwise comparisons. We showed that oronasal masks were associated with higher residual AHI, CPAP pressure and lower adherence compared with the nasal masks and pillows, while nasal masks had no significant difference compared with nasal pillows. Subgroup effects were observed when the residual AHI and CPAP pressure were measured during titration in the comparison of nasal masks versus oronasal masks. The meta-regression identified the lower pretreatment AHI, and the outcomes measured during titration were associated with lower CPAP pressure in nasal masks and nasal pillows compared with oronasal masks.

Our results showed nasal masks and nasal pillows offer modestly improved CPAP effectiveness by providing both better therapeutic efficacy (i.e. reduction of AHI), lower CPAP pressure and CPAP adherence compared with oronasal masks. The present study showed similar pairwise comparison results compared with Andrade's or Patil's meta-analyses (Table S7; R. G. S. Andrade et al., 2018; Patil et al., 2019), but we demonstrated a smaller but explicit improvement on adherence with nasal masks in both RCTs and non-RCTs. The difference may be due to more studies included and low heterogeneity (Figure S2c). Although a statistically significant difference exists, it remains debatable if these differences in CPAP adherence are of clinical significance (Patil et al., 2019).

Regarding the subgroup analysis and meta-regression, the differences in CPAP pressure were significant only in the non-RCTs subgroup with high heterogeneity, which might have resulted from a small number of participants in RCTs and the heterogeneity between the trials of each subgroup. This finding is similar to what R. G. S. Andrade et al. (2018) have reported. Another possibility was that in

FIGURE 7 Pairwise meta-regression to analyse the association between pretreatment apnea-hypopnea index (AHI) and differences in continuous positive airway pressure (CPAP) pressure among masks: (a) nasal mask versus oronasal mask; (b) nasal pillow versus oronasal mask; and (c) nasal mask versus nasal pillow



a couple of non-RCT studies, the pretreatment AHI for oronasal masks was a bit higher than nasal masks and nasal pillows, which may contribute to the higher residual AHI of oronasal masks (Table S2a).

We identified in this analysis that the pressure difference between nasal masks and oronasal masks measured during titration was greater than that measured during home CPAP therapy, which has not been previously reported. One possible explanation for the larger pressure difference during CPAP titration is that patients who received oronasal masks due to mouth breathing may convert to nasal breathing during CPAP therapy and thus required lower therapeutic pressure to keep upper airway patent (Bachour & Maasilta, 2004). Another contributing factor could be the wide range of home CPAP therapy duration (Table S2b), which may have dampened the mask-related difference in pressure.

Several possible mechanisms may lead to the poorer performance of oronasal masks than the nasal interfaces. First, oronasal masks have been shown to posteriorly displace the mandible, tongue and soft palate, and thus compromise the upper airway (R. G. Andrade et al., 2014; Bachour & Maasilta, 2004; Madeiro et al., 2019; Westhoff & Litterst, 2015). Second, positive airway pressure transmitted through the oral route may neutralize the upper airway splinting brought by positive airway pressure delivered through the nose and increase the upper airway surface tension (R. G. Andrade et al., 2014; Schorr, Genta, Gregorio, Danzi-Soares, & Lorenzi-Filho, 2012).

We did not meta-analyse the leaks as mask leaks are reported in different manners by the CPAP manufacturers, which makes the outcome assessment less robust. Multiple studies have shown that oronasal masks may be associated with higher unintentional leaks, thus leading to poor adherence (R. G. S. Andrade et al., 2018; Bachour & Maasilta, 2004; Schorr et al., 2012). In contrast, a recent study demonstrated oronasal masks can effectively reduce unintentional oral air leaks (Lebret et al., 2018). In clinical practice, meticulous mask fitting and refitting are crucial, and mask selection must be individualized.

The strengths of the present study included the application of NMA analysis as well as the use of subgroup analysis and meta-regression to clarify the factors contributing to the differences among nasal interfaces. NMA allows both direct and indirect comparisons across multiple studies with more than two different interventions, and has advantages over pairwise meta-analysis in resolving inconsistent outcomes from multiple studies. Also, NMA can increase statistical power and cross-validate the observed treatment effect of weak connections with reasonable network connectivity and sufficient sample sizes. There are a couple of limitations to this study. First, there was high heterogeneity among studies for outcomes including residual AHI and CPAP pressure, which made the quality of evidence low in those outcomes. Second, the outcomes in all of the included studies were measured during a short-term CPAP treatment (Table S2b), and the results may not reflect the long-term differences among masks. Third, we did not analyse the association between the mask manufacturers and outcomes, so it is not clear if the differences in manufacturers across the studies would be one of the sources of heterogeneity.

5 | CONCLUSION

Both NMA and pairwise comparison showed that nasal masks and pillows are overall better nasal interfaces than oronasal masks, especially in patients with lower pretreatment AHI and those with the therapeutic CPAP pressure determined during CPAP titration.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, PLL; methodology, PLL and MTL; software, YKT, SWH and LYC; formal analysis, YKT, SWH, LYC and YHC; writing—original draft preparation, SWH and LYC; writing—review and editing, PLL and AC; visualization, SWH, LYC and YHC; supervision, project administration and funding acquisition, PLL.

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DATA AVAILABILITY STATEMENT

Data available in article supplementary material

ORCID

Pei-Lin Lee  <https://orcid.org/0000-0002-6883-9502>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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