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Title: Is Humidified Better than Non-humidified Low Flow Oxygen Therapy? A Systematic Review and Meta-Analysis

Running title: Humidified & non-humidified oxygen

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Abstract

Aims: To determine the effects of low-flow oxygen therapy with humidified or non-humidified oxygen in adult patients.

Background: Although non-humidified oxygen in low-flow oxygen therapy is recommended by many guidelines, humidifying oxygen regardless of oxygen flow has been routinely performed in China and Japan and further studies are needed to evaluate the evidence.

Design: A systematic review and meta-analysis that comply with the recommendations of the Cochrane Collaboration were conducted.

Data Sources: Studies (1980–2016) were identified by searching PUBMED, EMBASE, Science Direct, Cochrane library, CNKI and Wanfang Database.

Methods: We performed a comprehensive, systematic meta-analysis of randomized controlled trials on the efficacy of humidified and non-humidified low-flow oxygen therapy. Summary risk ratios or weighted mean differences with 95% confidence intervals were calculated using a fixed- or random-effects model.

Results: Twenty-seven randomized controlled trials with a total number of 8876 patients were included. Non-humidified oxygen offers more benefits in reducing the bacterial contamination of humidifier bottles, as shown by the mean operating time for oxygen administration and the respiratory infections compared with humidified oxygen therapy. No significant differences were found in dry nose, dry nose and throat, nosebleed, chest discomfort, the smell of oxygen and SpO_2 changes.

Conclusions: The routine humidification of oxygen in low-flow oxygen therapy is not justifiable and non-humidified oxygen tend to be more beneficial. However, considering that the quality of most included studies is poor, rigorously designed, large-scale randomized controlled trials are still needed to identify the role of non-humidified oxygen therapy.

Keywords: care, humidification, meta-analysis, nurse, oxygen, review, nurses, nursing

Summary Statement

Why is this research or review needed?

- Long-term and low-flow oxygen administration benefits many patients and is widely used in hospital and community settings.
- The related guidelines recommend non-humidified oxygen if it is supplied to adults by nasal cannula at low flow rate. However, in China and some other countries, oxygen has been routinely humidified regardless of the oxygen flow rate.
- The evidence on the efficacy and effectiveness of oxygen humidification is lacking and warrants further investigation.

What are the key findings?

- Non-humidified oxygen seems to be more beneficial than humidified oxygen in low-flow oxygen therapy in adult populations.
- Some environmental and individual factors should be considered when choosing whether to humidify oxygen.

How should the findings be used to influence policy/practice/research/education?

- Rigorously designed and high-quality large-scale randomized controlled trials are needed to identify the efficacy and effectiveness of non-humidified and humidified oxygen therapy in children and adults.

- Incorporating this evidence into related nursing guidelines and translating it to clinical applications should be promoted.

INTRODUCTION

Oxygen therapy is the administration of oxygen at higher concentrations than ambient air (20.9%) for combating hypoxia (Fulmer and Snider 1984). Previous studies (Ringbaek et al. 2002, Heiring et al. 2015) have revealed that long-term and low-flow oxygen administration in some chronic diseases (such as chronic obstructive pulmonary disease (COPD)) can not only improve hypoxia symptoms but also reduce the length of hospital stay and prolong life expectancy. Nasal cannulas are the most widely used tool for oxygen administration in hospital and community, the oxygen delivered by nasal cannulas may or may not be humidified by humidifier bottles. Notably, oxygen is routinely humidified clinically in China and Japan (Miyamoto 2004, Li et al. 2010a) whenever low- or high-flow oxygen therapies are administered; however, in Europe and North America, oxygen is not humidified in low-flow oxygen therapy (<5 L/min) (O'Driscoll et al. 2008, 1995). The AARC clinical practice guideline (2007 revision and update) has suggested that the humidification of oxygen is unnecessary if it is supplied to adults by nasal cannula at flows ≤4 L/min (Aarc 2007). Nonetheless, several guidelines support the humidification of inhaled oxygen in long-term and low-flow oxygen therapy (Magnussen et al. 2001, O'Reilly and Bailey 2007). Therefore, the efficacy and effectiveness of humidifying oxygen in low-flow oxygen therapy warrants further investigation.

Background

Considering the significance of this issue, the review authors found that many randomized controlled trials (RCTs) on the superiority of humidified and non-humidified oxygen in low-flow oxygen therapy have been performed, yet a meta-analysis synthesizing these data to provide robust evidence is lacking. Two previous Chinese meta-analyses (Chu and Chen 2016, Ren et al. 2016) have concluded that non-humidified oxygen appears to be more beneficial than humidified oxygen in low-flow oxygen therapy, but the included data were all from Chinese papers and the sample sizes of the included RCTs were small. Recently, several related RCTs that investigated this issue have been performed and published, thereby warranting a larger-sized meta-analysis.

THE REVIEW

Aims

We performed this systematic review and meta-analysis of RCTs with the following aims: (1) to review the current evidence on the oxygen humidification in low-flow oxygen therapy; (2) to compare the efficacy of humidified and non-humidified oxygen in low-flow oxygen therapy; and (3) to analyze and conclude the appropriateness of oxygen humidification in low-flow oxygen therapy.

Design and review methods.

This systematic review and meta-analysis was conducted in concordance with recommendations from the Cochrane Collaboration(Higgins and Green 2011).

Search methods

We planned, performed and reported this meta-analysis in compliance with the PRISMA guideline (Liberati et al. 2009). Related articles that have been either published in English or Chinese (1980 to 2016) were identified and selected by searching PUBMED, EMBASE, Science Direct, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI) and Wanfang Database using the following search terms: 'oxygen inhalation therapy,'' 'oxygen inhalation '', 'oxygen therapy,' 'humidification'', 'humidified,'' 'non-humidified,' 'dried,' 'low flow,'' and 'low concentration.' We combined these terms in accordance with the instructions of the database (Wen, Wang and Zhang). In addition, the reference lists of the retrieved studies and previous reviews and meta-analyses were reviewed and manually searched (Wen and Wu) and we made no attempts to identify unpublished reports.

Study selection

Study selection was made based on the first screening of identified titles or abstracts and on a second check-up of full-text articles (Wen, Wang and Zhang). Studies were considered to be eligible if the following criteria were met: (1) RCTs or quasi-RCTs design; (2) adult population but not neonates or children; (3) studies were conducted in the hospital regardless of confinement in regular, emergency, or intensive care units; (4) study subjects have received low-flow oxygen therapy (≤5L/min); (5) containing the comparison groups of humidified and non-humidified oxygen administration; and (6) reporting the relative outcome data (complications like dry nose and throat and others).

Quality appraisal

The Cochrane Collaboration's 'risk of bias' tool was adopted for evaluating the methodological quality and risk of bias of included RCTs. Seven specific domains were examined and measured in this tool, as follows: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other' issues. Every domain can be classified as 'low risk of bias,' 'high risk of bias,' or 'unclear risk of bias' in accordance to the judgment criteria (Cochrane Handbook for Systematic Reviews of Intervention. Part 2: 8.5). Two reviewers (Wen and Wu) decided on the assessment and any dispute was solved by further discussion.

Data extraction

The following data were extracted by two reviewers independently (Wen and Wang): first author, year of publication, study design, patient population, oxygen administration (time, humidified fluid, oxygen flow), main outcomes and study results. The studies selection and data extraction were conducted by two authors independently and discussions resolved disagreements.

The main outcomes included: (1) dry nose; (2) dry throat; (3) nosebleed; (4) chest discomfort; (5) the smell of oxygen during oxygen therapy; (6) bacteria contaminations of humidifier bottles; (7) the mean operating time for oxygen administration; (8) respiratory infections; (9) others (the cost of oxygen therapy and others).

Data synthesis and analysis

All the extracted data were entered in the freeware program, Review Manager (RevMan) Version 5.3. The data input was conducted and double-checked by two researchers (Wen and Zhang), the data syntheses and interpretation were also performed by two authors (Wen and Shen) to ensure the accuracy of results. Binary outcomes were presented as Mantel–Haenszel-style odd ratios (ORs) with 95% confidence intervals and continuous outcomes were reported as inverse variance weighted mean differences (WMDs). A fixed-effect model was adopted in cases of homogeneity (P value of χ^2 test >0.10 and I^2<50%), whereas a random-effects model was used in cases of obvious heterogeneity (P value of χ^2 test >0.10 and I^2>50%). Publication bias was evaluated by using funnel plots and asymmetry was assessed by the Egger regression test (P value of <0.1 was considered to be significant for funnel plot asymmetry).

RESULTS

A total of 417 relevant publications were identified by comprehensive search and the abstracts of all citations were obtained. We included 64 potentially related studies for further full-text review. After further screening and quality appraisal on those studies, we included 27 RCTs for synthesized analysis (Figure. 1).

Study characteristics

The basic characteristics of 27 included studies are shown in Table 1. In brief, for all the included studies, a total of 8876 patients were involved, with 4583 for non-humidified oxygen administration and 4293 for humidified oxygen administration. Most studies were conducted in China, with sample sizes ranging from 18 to 997. The study settings also varied considerably. For oxygen administration, most studies focused on the time point of longer than 24 h and they chose sterile distilled water or sterile water for use as the humidifier fluid. The oxygen flow was all lower than 5 L/min. For outcome measurements, some subjective indices such as the feeling of non-humidified nose and throat and chest discomfort were included for analysis. Some objective outcomes such as bacteria contaminations of humidifier bottles and the mean operating time for oxygen administration were collected.

Figure 2 illustrates the risk of bias of the included RCTs. Even if all 27 included RCTs mentioned randomization, only 12 provided a detailed description of the methods used to produce the random sequence. Among them, some studies reported quasi-randomization methods, such as assigning patients into non-humidified oxygen group or humidified group according to the odd or even property of admission date (Chen and Guo 2015, Chen et al. 2012). In general, sequentially numbered, opaque, sealed envelopes were assigned to each participant to avoid selective bias; only four RCTs (Andres et al. 1997, Franchini et al. 2016, Liu and Chen 2015, Zeng et al. 2009) described adequate allocation concealments. Adequate blinding, which is adopted for personnel, participants and outcome assessment, is used to

prevent against bias. Nevertheless, as a simple and practical intervention, it seems to be impossible to blind participants to oxygen administration. For most included studies, no details on allocation concealment were reported, only two RCTs (Andres et al. 1997, Yang et al. 2014) have reported a blinding design on participants and outcome assessment. Most included studies reported completed outcome data (low risk of bias). Verification on selective reporting of outcomes are necessary because it may help evaluate the integrity of outcome reporting and protect against bias; three studies (Tian et al. 2012, Zeng et al. 2009, Zhou et al. 2015) appeared to selectively report the outcomes, because the outcomes of their studies were rather simple and limited. No other significant biases were found. The overall risk of bias is shown in Figure 3

Main analysis

The incidence of dry nose Four studies(Andres et al. 1997, Chen et al. 2012, Tian et al. 2012, Yang and Yu 2015) reported the incidence of dry nose after oxygen administration; the summary OR on the incidence of dry nose was 1.21 (95% CI: 0.76-1.93), with evidence of heterogeneity (P = 0.07, I^2 = 58%) (Fig. 4A).

The incidence of dry nose and throat Nine studies (Cai et al. 2013, Chen and Guo 2015, Han 2011, Li et al. 2010b, Li et al. 2015, Liu and Chen 2015, Yue et al. 2015, Zeng et al. 2009, Yuan et al. 2013) reported the incidence of dry nose and throat after oxygen administration; the summary OR on the incidence of dry nose and throat was 0.93 (95% CI: 0.78-1.10), with no evidence of heterogeneity (P = 0.35, I^2 = 10%) (Fig. 4B).

The incidence of cough Two studies (Andres et al. 1997, Franchini et al. 2016) reported the incidence of cough after oxygen administration; the summary OR on the incidence of cough was 0.80 (95% CI: 0.42-1.52), with no evidence of heterogeneity ($P = 0.17$, $I^2 = 46\%$) (Fig. 2C).

The incidence of nosebleed Six studies (Andres et al. 1997, Chen et al. 2012, Liu and Chen 2015, Wu 2016, Yuan et al. 2013, Yue et al. 2015) reported the incidence of nosebleed after oxygen administration; the summary OR on the incidence of nosebleed was 1.34 (95% CI: 0.77-2.34), with no evidence of heterogeneity ($P = 0.82$, $I^2 = 0\%$) (Fig. 4D).

The incidence of chest discomfort Four studies (Andres et al. 1997, Chen et al. 2012, Yuan et al. 2013, Yue et al. 2015) reported the incidence of chest discomfort after oxygen administration; the summary OR on the incidence of chest discomfort was 0.91 (95% CI: 0.53-1.55), with no evidence of heterogeneity ($P = 0.59$, $I^2 = 0\%$) (Fig. 4E).

Bacteria contaminations of humidifier bottles Eight studies (Haung et al. 2014, Li et al. 2011, Li et al. 2015, Lou et al. 2016, Ning et al. 2014, Yang et al. 2015, Yang and Yu 2015, Zhou et al. 2015) reported the bacterial contamination of humidifier bottles after oxygen administration; the summary OR on the bacteria contamination of humidifier bottles was 0.16 (95% CI: 0.06-0.43), with evidence of heterogeneity ($P < 0.01$, $I^2 = 90\%$) (Fig. 5A).

The mean operating time for oxygen administration(seconds) Six studies (Chen and Guo 2015, Huang et al. 2014, Lou et al. 2016, Tian et al. 2012, Yang et al. 2015, Zheng et al. 2015) reported the mean operating time for oxygen administration, the summary WMD on mean operating time (seconds) for oxygen administration was −35.84 (95% CI: −44.51 - −27.17), with evidence of heterogeneity ($P < 0.01$, $I^2 = 99\%$) (Fig. 5B).

The smell of oxygen Four studies (Chen et al. 2012, Liu and Chen 2015, Yuan et al. 2013, Yue et al. 2015) reported the smell of oxygen after oxygen administration; the summary OR on smell of oxygen was 1.35 (95% CI: 0.69-2.65), with no evidence of heterogeneity ($P = 0.41$, $I^2 = 0\%$) (Fig. 5C).

SpO_2 Two studies (Cai et al. 2013, Wu 2016) reported SpO_2 after oxygen administration, the summary WMD on SpO_2 was −0.60 (95% CI: −3.32-2.21), with evidence of heterogeneity ($P <0.01$ $I^2 = 97\%$) (Fig. 5D).

Respiratory infections Four studies (Huang et al. 2014, Yang et al. 2015, Yue et al. 2015, Zhou et al. 2015) reported the respiratory infection after oxygen administration; the summary OR on respiratory infection was 0.39 (95% CI: 0.21-0.73), with no evidence of heterogeneity ($P = 0.14$, $I^2 = 45\%$) (Fig. 5E).

Subgroup and sensitivity analyses

No subgroup analyses were performed in this study. Sensitivity analyses, which investigate the influence of a single study on the overall risk estimate by abandoning one study in each turn, suggested that the overall risk estimates do not substantially change by any single study.

DISCUSSION

Findings from our meta-analysis indicate that non-humidified and humidified oxygen in low-flow oxygen administration provide no effect differences on dry nose, dry nose and throat, nosebleed, chest discomfort, smell of oxygen and SpO_2 after oxygen administration, but non-humidified oxygen provide more beneficial effects on the reduction of the bacterial contamination of humidifier bottles, shortening the mean operating time for oxygen administration and decreasing respiratory infections. Therefore, the use of non-humidified oxygen seems to be better than humidified oxygen in low-flow oxygen therapy. However, considering the quality of most included RCTs is poor, our results should be interpreted with caution.

In the past decades, humidification of the inhaled oxygen in low-flow oxygen therapy was considered unnecessary given that oxygen is not readily soluble in water (Miyamoto 2004). The routinely used cold bubble humidification for oxygen administration may not actually

work (Vargas and Esquinas 2016). A recent critical study (Franchini et al. 2016) demonstrated that the cold bubble humidification does not humidify inspired oxygen at all and offers no benefits in the promotion of mucociliary clearance, mucus hydration and pulmonary function. Therefore, many related guidelines (O'Driscoll et al. 2008, 1995, Aarc 2007) have recommended the direct use of non-humidified oxygen in low-flow oxygen therapy. This may explain why the recent studies on this issue are quite few in European and American areas; however, in China and Japan, humidification of oxygen in clinic is still routinely performed whether the oxygen flow is low or high (Miyamoto 2004, Li et al. 2010a). Many Chinese medical researchers have investigated this issue in the past few years as this situation warrants changes.

Patients receiving low-flow oxygen therapy by nasal cannula actually only inhale 2.4-19% of provided oxygen because the upper respiratory tract can provide 75% heat and moisture to make the inhaled air comfortable for us (Branson 1998). Additionally, the relative humidity of inhaled air is more important than absolute humidity; the discomfort caused by non-humidified oxygen to patients is far lower than the indoor air brings (Sottiaux 2006). This may explain the results that non-humidified and humidified oxygen produce no significant difference on the complications, such as the incidence of non-humidified nose, non-humidified throat, nosebleed and chest discomfort. However, these outcomes are rather subjective as the measurements on these outcomes are not accurate enough. Several studies (Campbell et al. 1988, Ning et al. 2014, Xia et al. 2014, Yang et al. 2014, Zheng et al. 2015) conducted classified evaluation on the severity of these symptoms, but due to the criteria requirements, we

did not include these data in the meta-analysis. Besides, non-humidified and humidified oxygen inhalation exerted similar effects on SpO_2, indicating similar therapeutic values. However, we only included two RCTs on this outcome. Further studies are needed to elucidate the differences in efficacy.

Our review revealed that non-humidified oxygen offers more advantages in reducing bacteria contaminations of humidifier bottles, the mean nursing operating time and respiratory infection without increasing the incidence of other complications. Respiratory infection leads the list of hospital-acquired infections. While bacteria contaminations of humidifier bottles are closely related to respiratory infection (Kobayashi et al. 2006), the wet condition of humidifier bottles with water inside may be more adaptable to bacteria proliferation. A survey (Li et al. 2010a) reported that the bacteria contamination rate of humidifier bottles with water inside after 24-h oxygen therapy reached 57.5%, yet the non-humidified oxygen group is only 44.2%, with the top three bacteria being *Staphylococcus aureus*, *Escherichia coli* and *Bacillus*. The contamination of humidifier bottles possibly increases the risk for respiratory infection with the inhalation of contaminated oxygen. Ideally, the non-humidified oxygen requires no addition or change of sterile water, which can significantly reduce the operating time for oxygen therapy, thereby relieving the nursing workload and decreasing the medical expenditure. Our results on the bacterial contamination of humidifier bottles and the mean nursing operating time are significantly heterogeneous. These outcomes should be interpreted

carefully as the possible causes of the heterogeneity may be the difference on the nursing intervention and operating time calculation. Some of the included RCTs did not indicate the accurate oxygen flow in the inhalation therapy, possibly contributing to the results' heterogeneity.

Although our results support the non-humidified oxygen application in the low-flow oxygen therapy, several details should be taken into consideration. No significant change in airway humidity was observed when oxygen was given pre-nasally without humidification (Dellweg et al. 2013). The room air humidity may act as an important factor. A Chinese survey in Xinjiang, northwest area with non-humidified climate of China found that non-humidified oxygen leads to more complications when compared with the humidified oxygen in low-flow oxygen therapy (Yang et al. 2014). Hence, we should take air humidity into account when performing oxygen therapy. Besides, more studies are needed to address other possible effects achieved with humidified oxygen administration, such as the clarification of the effect of humidified oxygen on the recovery of patients with chest disease. Also, as the relative risks/benefits of high versus low oxygen therapy and humidified versus non-humidified oxygen therapy in child and adult remain different (Nath et al. 2010), more individual factors should be considered.

Considering that only three fair-quality RCTs (Andres et al. 1997, Franchini et al. 2016, Yang et al. 2014) were included, sensitivity analysis of those better quality studies should be performed. Those studies that used sound designs for the method of randomization and

blinding are likely to have less risk of bias. Andres (Andres et al. 1997) recommended that accepting non-humidification as the standard method for delivering low-flow oxygen therapy may decrease the patient's risk of developing nosocomial pneumonia, reduce expenditures for oxygen therapy and eliminate one source of biomedical waste. However, the study of (Franchini et al. 2016) showed that unheated bubble humidification does not humidify inspired oxygen to prevent deterioration of mucociliary clearance, mucus hydration and pulmonary function; this may support the finding that humidification performed no better than non-humidification, which is consistent with Andres's results (Andres et al. 1997). Yang et al. (Yang et al. 2014) found that the dryness of oropharyngeal condition is related to the humidification, but the study was conducted in the dry area of China and the data are limited for our synthesized analysis; these results should be interpreted with caution. Similarly, (Andres et al. 1997) also found that the mean symptom scores for nasal dryness in humidification group were significantly lower than the non-humidification group. Therefore, as the effect of cold bubble humidification works remain conflicting and future studies should focus more on this problem.

Several limitations in this review should be noted. First, as most included RCTs were conducted in China, population differences may exist. Second, the quality of included studies is disturbing as most studies do not use a blind design on the allocation concealment and participants. For some studies with a blind design, the authors only state that treatment allocation is concealed without providing details on how this was performed. The lack of blinding design on participants and personnel may lead to significant bias. Future studies

should focus more on study design. Third, due to data limitation, we did not perform subgroup analysis and funnel plot. Some of our results exhibited evident heterogeneity, with the possible causes of the heterogeneity difficult to identify. Finally, targeted on adult population, our findings are unlikely to be relevant to neonates or children, a separate analysis to establish benefits and harms for these specific population groups is needed.

CONCLUSION

Non-humidified oxygen appears to be of greater benefit than humidified oxygen in low-flow oxygen therapy. However, some environmental and individual factors should be considered when considering the necessity of humidifying oxygen. Meanwhile, considering that our results are based on poor quality and heterogeneous trial evidence, the results should be interpreted with caution despite our significant results. Future studies should focus more on the study design (randomization, allocation, blinding, outcomes evaluation and interpretation) to provide more insights and evidence into this issue.

Author Contributions:

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE*):

1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;

2) drafting the article or revising it critically for important intellectual content.

* http://www.icmje.org/recommendations/

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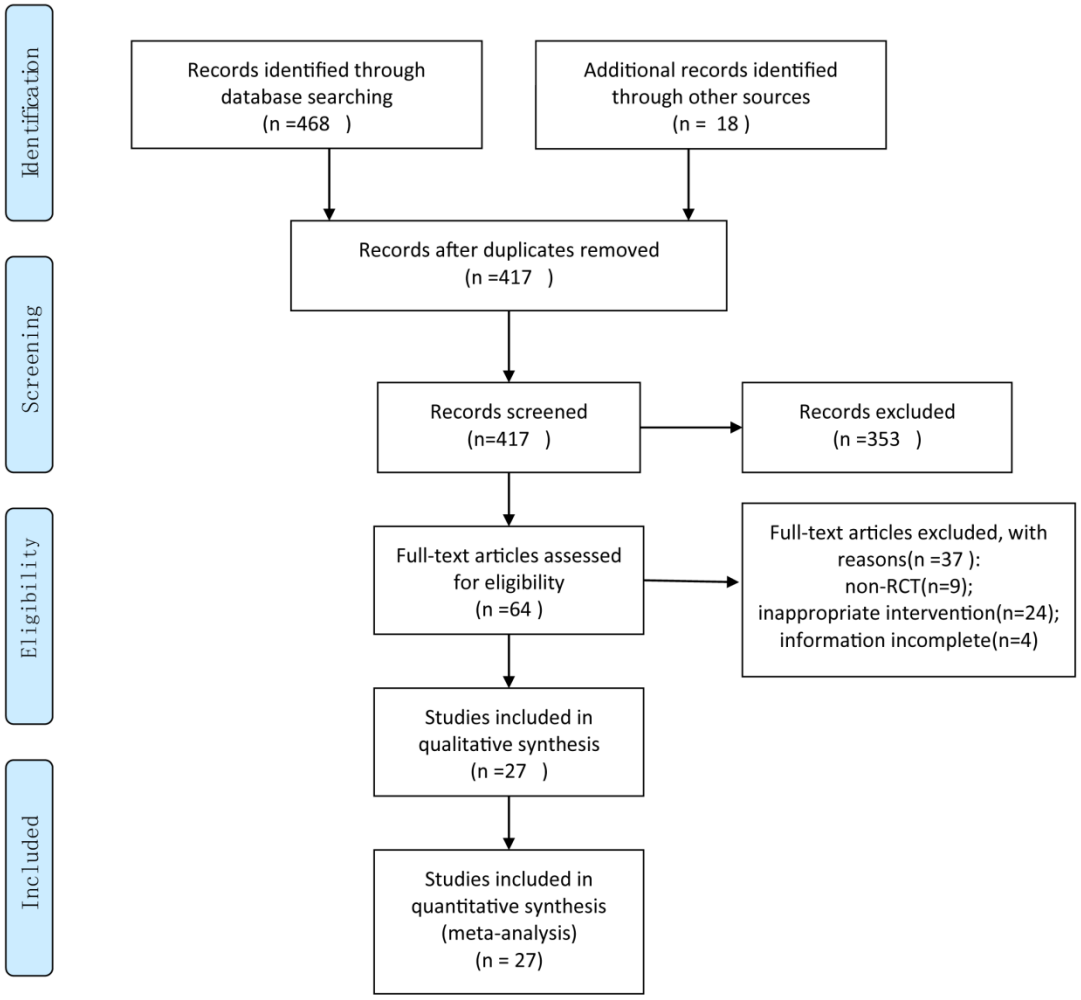
Table 1 The characteristics of included studies

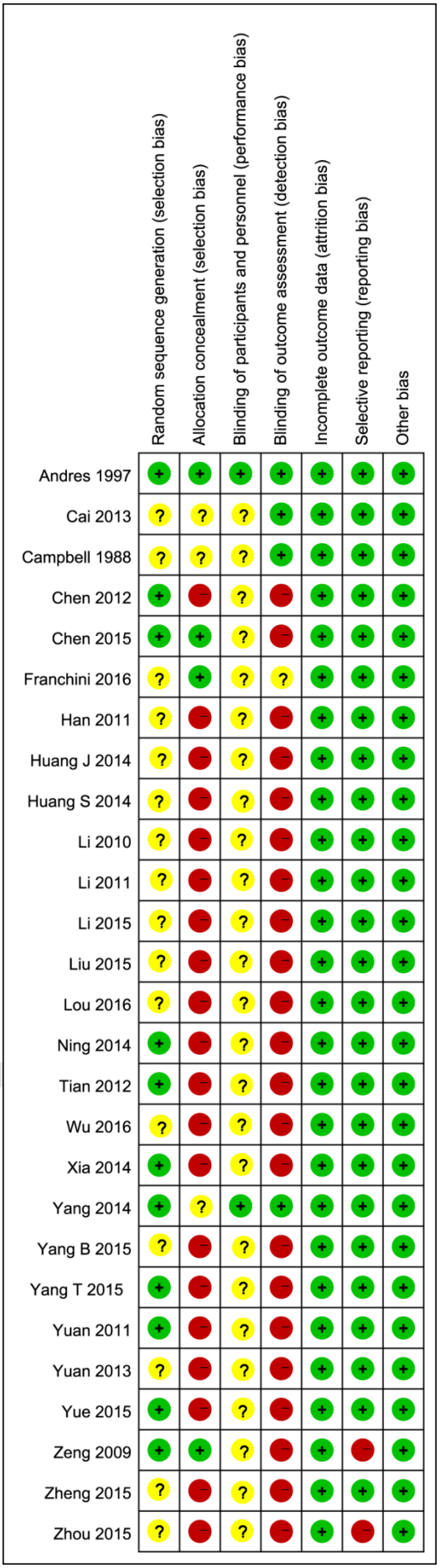
Study(author year)	Country	Sample（T/C）	Department	Intervention			Outcomes
				Time for oxygen administration	Fluid for oxygen humidification	Oxygen flow	
Andres 1997(Andres et al., 2016)	Canada	126/111	NA	>2d	NA	<4L/min	a, b, c, d, e, f
Campbell 1988(Campbell et al., 1988)	USA	86/99	Respiratory department	NA	NA	5L/min	a, b, c, d, e
Franchini 2016(Franchini et al., 2016)	Brazil	10/8	Basic health units/Pulmonary outpatient clinic	>12h	NA	NA	f, g
Cai 2013(Cai et al., 2013)	China	51/29	Veteran ward	>4d	SDW	NA	a, b, j, k
Zeng 2009(Zeng et al., 2009)	China	30/30	Neurosurgery department	>5d	SDW	NA	a, b
Chen 2015(Chen and Guo, 2015)	China	328/352	Emergency department	NA	SDW	NA	a, b, c, d, i, k, l
Chen 2012(Chen et al., 2012)	China	235/245	Cadiovascular department	>12h	SDW	<4L/min	a, b, c, d, e, h
Han 2011(Han,	China	400/40	Respiratory	>24h	NA	4L/min	a, b, k

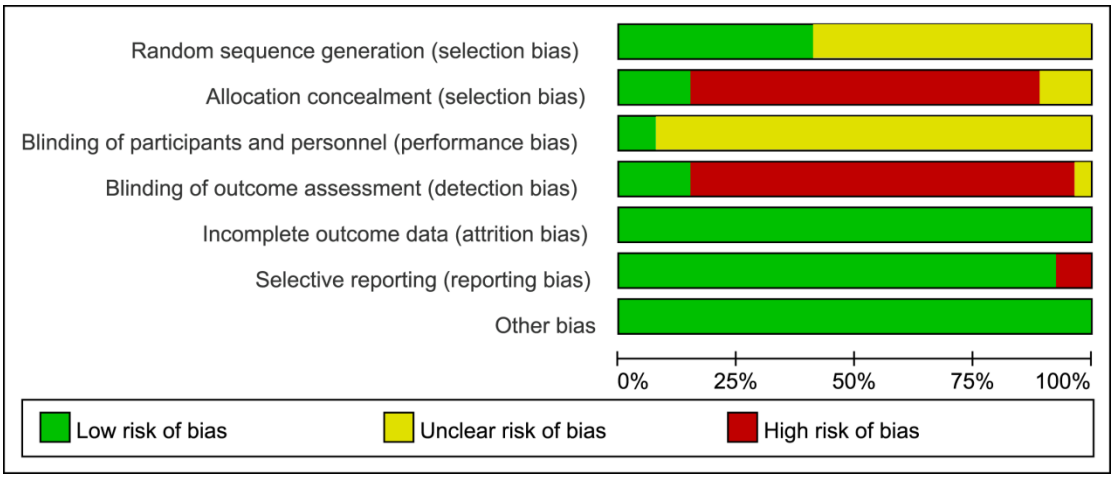
2011)		0	department				
Huang J 2014(Haung et al., 2014)	China	40/40	Blood purification center	NA	SDW	1～4 L/min	a, e, i, k
Huang S 2014(Huang et al., 2014)	China	507/490	Cadiovascular department	>12h	NA	<4L/min	a, b, c, l, m
Li 2010(Li et al., 2010)	China	418/348	Neurosurgery /respiratory department	>12h	NA	<4L /min	a, b, c, d, e, h
Li 2011(Li et al., 2011)	China	130/130	NA	>7d	SDW	NA	a, b, i, k
Li 2015(Li et al., 2015)	China	173/168	NA	>72h	SDW	<4L /min	a, b, k
Liu 2015(Liu and Chen, 2015)	China	174/174	The dialysis center	3~ 4.5 h	SDW	NA	a, b, e, i
Lou 2016(Lou et al., 2016)	China	101/99	Orthopedic department	NA	SDW	<4L /min	a, b, d, i, k, l
Ning 2014(Ning et al., 2014)	China	201/199	ICU	>24h	SDW	≤ 4 L/min	a, i, k, l
Tian 2012(Tian et al., 2012)	China	316/218	CCU	≥72 h	SDW	<4L /min	a, b, l
Wu 2016(Wu, 2016)	China	90/90	Respiratory department	24～72h	SDW	1-4 L/min	a, b, e, j, l, n, o
Xia 2014(Xia et al., 2014)	China	86/99	Emergency department	NA	NA	1～2 L/min	a, b, c, d

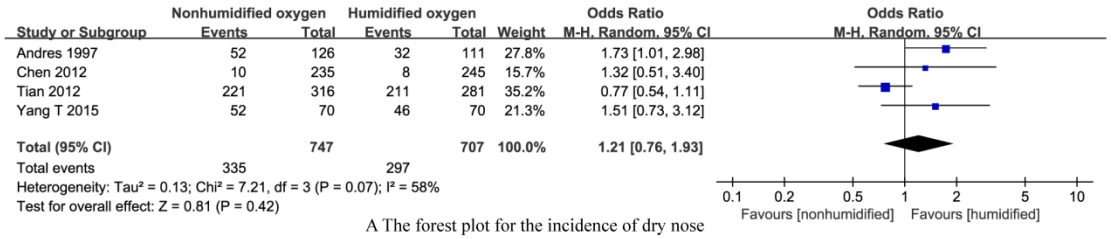
Yang 2014(Yang et al., 2014)	China	165/65	NA	>5 d	SDW	NA	a, b, c, d, h, i
Yang B 2015(Yang et al., 2015)	China	184/201	NA	>24h	NA	<4 L/min	a, b, d, h, i, k, l, m
Yang T 2015(Yang and Yu, 2015)	China	70/70	Emergency department	<48h	SDW	<4 L/min	a, b, k, l
Yuan 2011(Yuan et al., 2011)	China	72/78	Respiratory department	NA	SDW	≤4 L/min	a, b, d, i
Yuan 2013(Yuan et al., 2013)	China	256/230	NA	> 24 h	SDW	NA	a, b, d, e, i
Zheng 2015(Zheng et al., 2015)	China	60/60	Cadiovascular department	> 24 h	SDW	<4 L/min	a, b, d, e, g, h, i, l
Zhou 2015(Zhou et al., 2015)	China	50/50	Neurosurgery department	NA	SDW	1～4 L /min	k, m, p
Yue 2015(Yue et al., 2015)	China	224/210	Respiratory department	>5 d	SDW	2 L /min	a, b, d, h, i

Notes: NA, not available; SDW, sterile distilled water; a, non-humidified nose; b, non-humidified throat and non-humidified mouth; c, headache; d, chest discomfort; e, nosebleed; f, cough; g, sleep problems; h, nausea; i, the smell of oxygen during oxygen therapy; j, SpO_2; k, bacteria contaminations of humidifier bottles; l, the mean operating time for oxygen administration; m, respiratory infections; n, heart rate; o, respiratory rate; p, the cost of oxygen therapy.

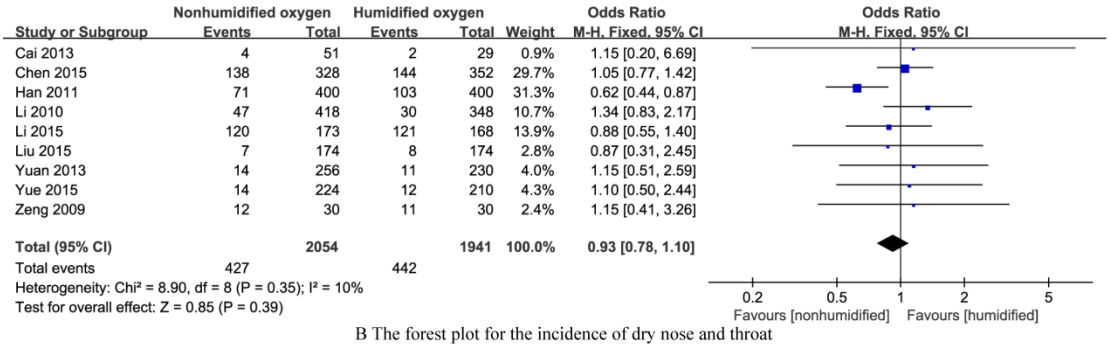




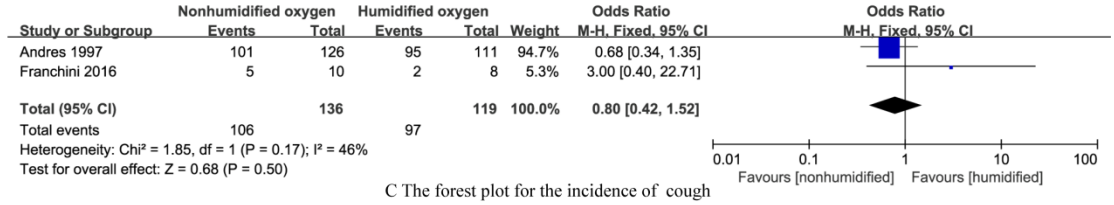




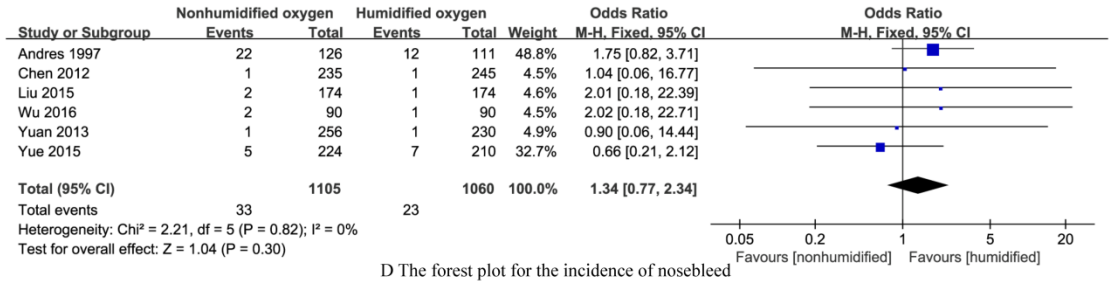
A The forest plot for the incidence of dry nose



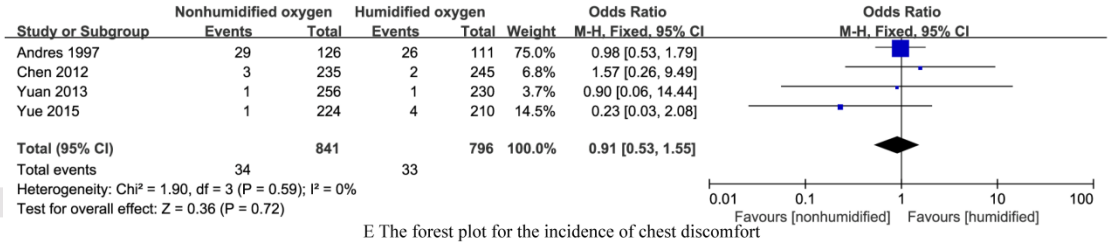
B The forest plot for the incidence of dry nose and throat



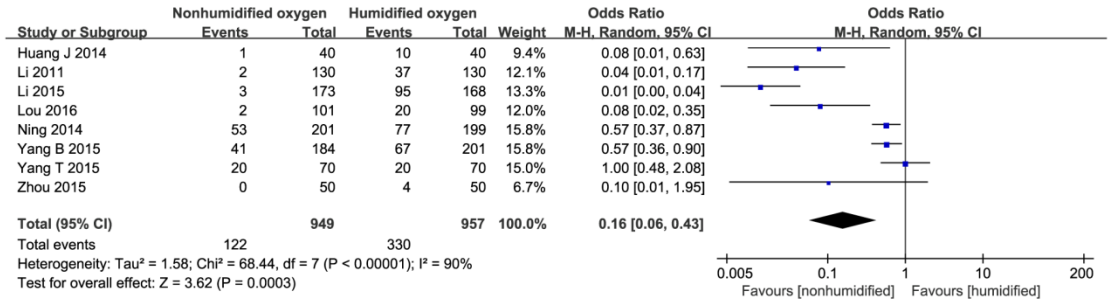
C The forest plot for the incidence of cough



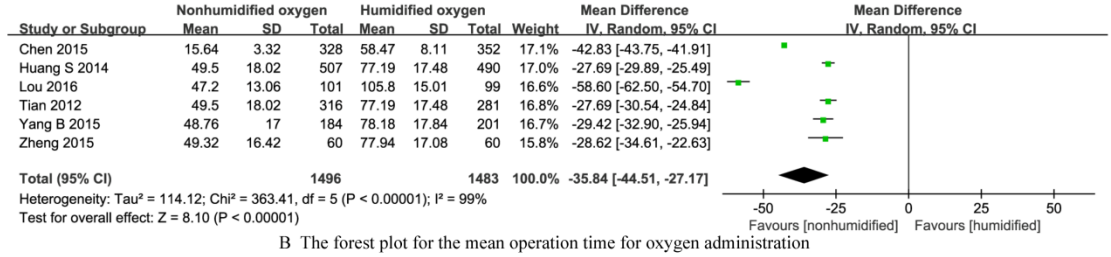
D The forest plot for the incidence of nosebleed



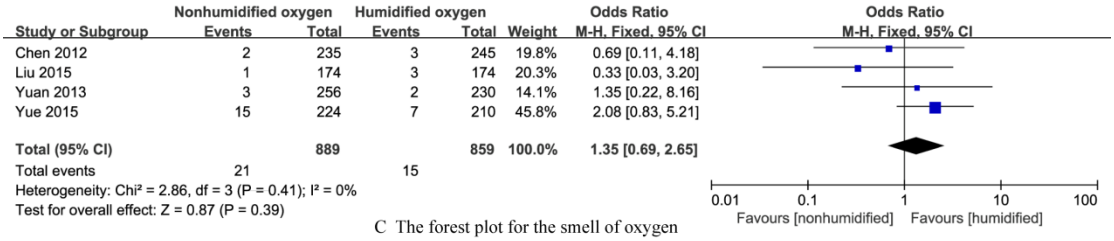
E The forest plot for the incidence of chest discomfort



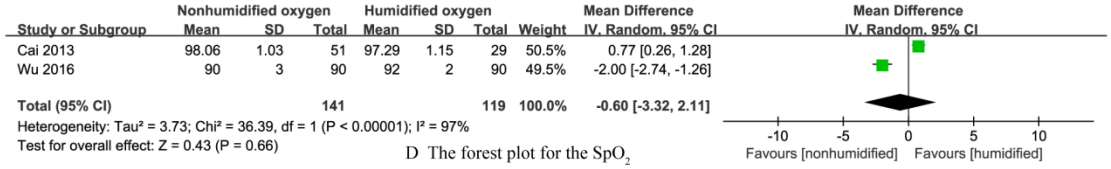
A The forest plot for bacteria contaminations of humidifier bottles



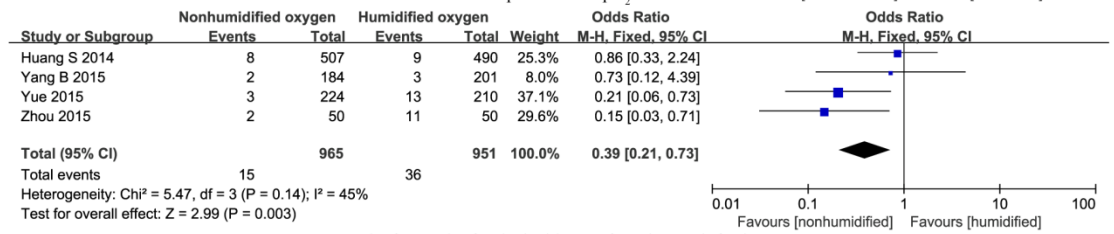
B The forest plot for the mean operation time for oxygen administration



C The forest plot for the smell of oxygen



D The forest plot for the SpO_2



E The forest plot for the incidence of respiratory infection