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Review article

Acupuncture for dyspnea and breathing physiology in chronic respiratory diseases: A systematic review and meta-analysis of randomized controlled trials

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A R T I C L E I N F O

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A B S T R A C T

Background: Dyspnea, a common symptom of chronic respiratory diseases (CRDs), is closely linked to higher levels of functional impairment and death, leading to significant societal and financial challenges. Despite numerous clinical trials and systematic reviews suggested the potential benefits of acupuncture for chronic obstructive pulmonary disease (COPD) and lung cancer, there is currently insufficient evidence to conclusively prove its effectiveness in alleviating dyspnea in patients with CRDs.
Methods: To compile and evaluate the existing data on the effectiveness and safety of acupuncture for managing dyspnea in CRDs. Randomized controlled trials investigating acupuncture for the treatment of dyspnea in patients with CRDs, such as COPD, lung cancer, asthma, bronchiectasis, interstitial lung disease, chronic pulmonary heart disease and bronchitis, were searched and retrieved from five electronic databases in English or Chinese.
Results: A total of 23 studies meeting the inclusion criteria were found in databases, covering various CRDs such as COPD, lung cancer, and asthma. A meta-analysis that compared acupuncture to a control group (which included no acupuncture and sham acupuncture) found significant advantages for acupuncture in reducing dyspnea severity ($P = 0.0003$), increasing 6MWD ($P < 0.00001$), improving quality of life measured by St. George's Respiratory Questionnaire ($P = 0.03$) and karnofsky performance status score ($P < 0.00001$). No significance was found in breathing physiology represented by FEV_1 ($P = 0.34$) and FVC ($P = 0.15$). There was a comparable incidence of negative outcomes in both groups ($P = 0.07$). Results were consistent when compared to sham acupuncture. In addition, subgroup analyses were also consistent when different diseases or types of acupuncture were analyzed.
Conclusions: Acupuncture may be an effective and safe non-pharmacological complementary intervention to relief dyspnea for patients with CRDs. Nevertheless, research with high quality and large sample sizes is needed for further investigation.

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1. Introduction

Chronic respiratory diseases (CRDs), among the four major human chronic diseases according to World Health Organization [1], are a group of diseases affecting the respiratory tract and related structures. The most prevalent types include chronic obstructive pulmonary disease (COPD), lung cancer, asthma, interstitial lung disease, bronchiectasis, cystic fibrosis, sleep apnea, tuberculosis, occupational lung disease and pulmonary hypertension. CRDs are a significant issue for public health, impacting around 544.9 million individuals in 2017 and leading to an estimated 3.91 million deaths, which accounts for roughly 7 % of global mortality [2,3]. Reducing morbidity, disability, and risk of death require effective treatments that manage symptoms, enhance quality of life (QoL), and prevent adverse outcomes for patients.

Dyspnea, which is described as "the subject experience of breathing discomfort", is a prevalent and distress symptom suffered by patients with CRDs [4]. More importantly, dyspnea is a standalone indicator of increased long-term death rates [5], and is linked to reduced ability to exercise and quality of life, as well as increased risk of hospitalization [6–9]. Advancements in research have greatly improved our understanding of the pathophysiology and neurophysiology of dyspnea, leading to the development of various pharmacological and nonpharmacological interventions like opioids, benzodiazepines, and antidepressants, as well as treatments such as oxygen therapy, non-invasive ventilation, and pulmonary rehabilitation [10]. Regrettably, certain therapies produce unsatisfactory or contradictory outcomes, or concentrate solely on the particular illness with restricted applicability, leading to missed chances to enhance patient treatment. For example, opioid use can alleviate shortness of breath in patients with advanced COPD, interstitial lung disease, and cancer, but it often leads to side effects such as nausea, vomiting, drowsiness, and constipation [11,12]. Hence, there is an urgent requirement to find alternative treatment approaches to improve the common occurrence of dyspnea in various chronic respiratory diseases.

Acupuncture, a non-pharmacological therapy often used in conjunction with western medicine, is commonly utilized for CRDs. Several randomized controlled trials (RCTs) have assessed how effective acupuncture is in reducing dyspnea in individuals with COPD [13–15]. A significant achievement in the acceptance of acupuncture for CRDs is the acknowledgment in the 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD) update that acupuncture can be beneficial for individuals with advanced COPD by potentially enhancing breathlessness and QoL [16]. A recent study showed that acupuncture could alleviate dyspnea in advanced conditions like COPD and lung cancer [17], however, it also included breast cancer and did not address studies conducted in Chinese. Acupuncture also showed improvement in asthma symptoms [18]. Thus, acupuncture has demonstrated encouraging therapeutic advantages for a range of CRDs. Despite the varied pathophysiological abnormalities associated with dyspnea in various CRDs, there is a shared pathogenesis among these diseases [19], including neuromechanical dissociation [4] and affective distress from anxiety, panic, and depression [20]. Acupuncture may play a role in treating these symptoms.

However, there is not enough proof and a lot of doubt surrounding the effectiveness and safety of acupuncture for treating CRDs. The unresolved and crucial question of whether acupuncture can improve dyspnea and objective breathing parameters, including lung function and exercise tolerance, is hindering its use in CRDs. There has not been a systematic review and meta-analysis published to answer the questions mentioned above. here is no published systematic review and meta-analysis to address above questions so far. This review aims to examine a wide range of CRDs and methodically assess the effectiveness of acupuncture in improving dyspnea and respiratory function in CRDs.

2. Methods

2.1. Protocol and Registration

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Available from: https://www.crd.york.ac.uk/prospero/#searchadvanced; Record No. CRD42020189624) [21] and conducted following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

2.2. Database and searching strategy

Reports of RCTs on acupuncture for CRDs were found in five electronic databases: MEDLINE (PubMed), EMBASE (Ovid), Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Library Database from inception until March 2023. The search languages included both English and Chinese. Furthermore, we also searched the database of ongoing clinical trials including the Chinese clinical trial registry (http://www.chictr.org.cn/) and the international clinical trial registry (http://clinicaltrials.gov/). Moreover, the additional relevant studies were also manually reviewed by using references contained in the previously published systematic reviews.

Keywords such as "acupuncture" or "needle" and "chronic respiratory diseases" or "COPD" or "emphysema" or "lung cancer" or "asthma" or "bronchiectasis" or "interstitial lung disease" or "chronic pulmonary heart disease" or "bronchitis" were used individually or in combination with their abbreviations or derivatives. Details of the search strategy used for each database were provided in Supplementary file 1.

2.3. Inclusion criteria

2.3.1. Type of studies

All RCTs that assessed any form of invasive acupuncture were incorporated, irrespective of blinding status. Reviews, case-control, case reports, or animal experiments were excluded.

2.3.2. Type of participants

Adults aged 18 and older with CRDs (including COPD, emphysema, lung cancer, asthma, bronchiectasis, interstitial lung disease, chronic pulmonary heart disease, bronchitis and etc.) of any gender, any profession or ethnicity or education or economic status were encompassed.

2.3.3. Type of interventions

Studies adopting acupuncture treatment of CRDs as experimental interventions were included. Control interventions included sham acupuncture and untreated blank controls. Studies comparing acupuncture with sham acupuncture or no acupuncture were investigated. The study examined different treatment comparisons including acupuncture versus no acupuncture, acupuncture versus placebo/false/sham acupuncture, and acupuncture combined with another basic therapy versus the therapy alone. Research on alternative techniques for activating acupuncture points, such as acupressure, laser stimulation, cupping, or transcutaneous electrical stimulation, was not considered. Pharmaco-acupuncture, acupoint injection and acupuncture combined with other Chinese medicine modalities, such as warm acupuncture technique (employing a needle with moxibustion on top) or acupuncture in conjunction with moxibustion, were excluded from the study.

2.3.4. Outcomes

Primary outcomes were as follows: (1) Dyspnea severity using various scoring systems including the visual analogue scale (VAS) [23], the Borg scale score and the modified Medical Research Council (mMRC) scale [24]; (2) Breathing physiology: lung function tests including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1% predicted.

Secondary outcomes were as follows: (1) Exercise tolerance: 6-min walk distance (6MWD); (2) QoL: measured by a validated questionnaire including St George's Respiratory Questionnaire (SGRQ) [25] and karnofsky performance status (KPS); (3) Adverse events.

2.4. Data collection and data extraction

Two reviewers independently assessed the titles and abstracts of search results using predetermined criteria to determine potential relevance. Full texts were reviewed for further screening. In addition to discussion between the two reviewers, a third reviewer was consulted to resolve differences between the texts. Each reviewer confirmed that all articles included in the review were eligible.

Data was extracted from standard database tables in Microsoft Excel using standardized template layouts. Data was gathered from qualifying research studies, including details on study structure, participant demographics, interventions, and results. Any discrepancies were resolved by consensus.

2.5. Risk of bias assessment and GRADE

The risk of bias in the studies included was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2) [26]. This scale evaluated five areas: bias from randomization, bias from deviations in interventions, bias from missing outcome data, bias in outcome measurement, and bias in reported result selection.

We evaluated the credibility of evidence for our main results using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [27]. In GRADEpro (https://gradepro.org/), we generated a GRADE summary table to summarize our results and GRADE ratings.

2.6. Data analysis

Continuous data was analyzed using the inverse variance method and a random-effects model to calculate the mean difference (MD) with 95 % confidence intervals (CI). For dichotomous data, risk difference (RD) with 95 % CI was summarized using Mantel and Haenszel method. Heterogeneity was investigated by I^2 statistic and the chi-squared test. The chi-squared test assesses whether observed differences in the results of the included studies are compatible with chance alone. The I^2 metric evaluates the proportion of variation in the effect estimates attributed to heterogeneity, with I^2 values of 25 %–50 % suggesting low heterogeneity, 50 %–75 % suggesting moderate heterogeneity, and >75 % indicating high heterogeneity, as reported in Ref. [28]. Statistical significance was determined for values with a P value less than 0.05.

In order to investigate additional sources of variation in the primary outcome, all studies that were included were categorized into subgroups based on the types of controls and various diseases. To check for publication bias, a funnel plot was created for each trial's effect size compared to the standard error, when there were at least 7 studies in the meta-analysis. For all statistical analyses, we utilized Review Manager 5.3 (Version 5.3.5) from Cochrane collaboration.

3. Results

3.1. Study selection

As shown in Fig. 1, 1765 possible records were found through database searching in August 2022 and updated in March 2023. After removal of duplicates, 1094 articles were screened for initial elimination and 1049 records were excluded because of certain reasons. After evaluating 45 records, 22 were excluded for reasons such as lack of eligibility (see Supplementary file 2). Finally, 23 studies met the criteria and were included in the final analysis.

3.2. Study characteristics

A review of the 23 clinical trials including 1098 patients was conducted in Tables 1 and 2. Eleven studies included patients with stable COPD [13–15,29–36], eight with asthma [37–44] and four with lung cancer [45–48]. Fifteen trials utilized a sham treatment involving various methods such as non-invasive or surface-level needles placed at real points, slightly offset points, or needling at irrelevant non-acupuncture locations.

Significant variation was observed in the acupuncture procedures utilized in each study. Variations encompassed the integration of acupuncture with additional treatments, the specific acupuncture points targeted during therapy, the length of stimulation, study duration, treatment regimen and follow-up. Five trials used acupuncture in conjunction with other techniques: two trials combined with pulmonary rehabilitation [29,33], and three trials with aerobic exercise [31,32,36]. The majority of studies had stimulation durations ranging from 15 to 30 min, with only two studies, Cheng (45min) [45] and Suzuki (50 min) [13], reporting longer periods of stimulation. Most of the trials mentioned particular acupuncture points in their interventions, with only two utilizing a flexible protocol rooted in traditional Chinese medicine principles that integrate both the five-element and eight-condition theories [14,41].

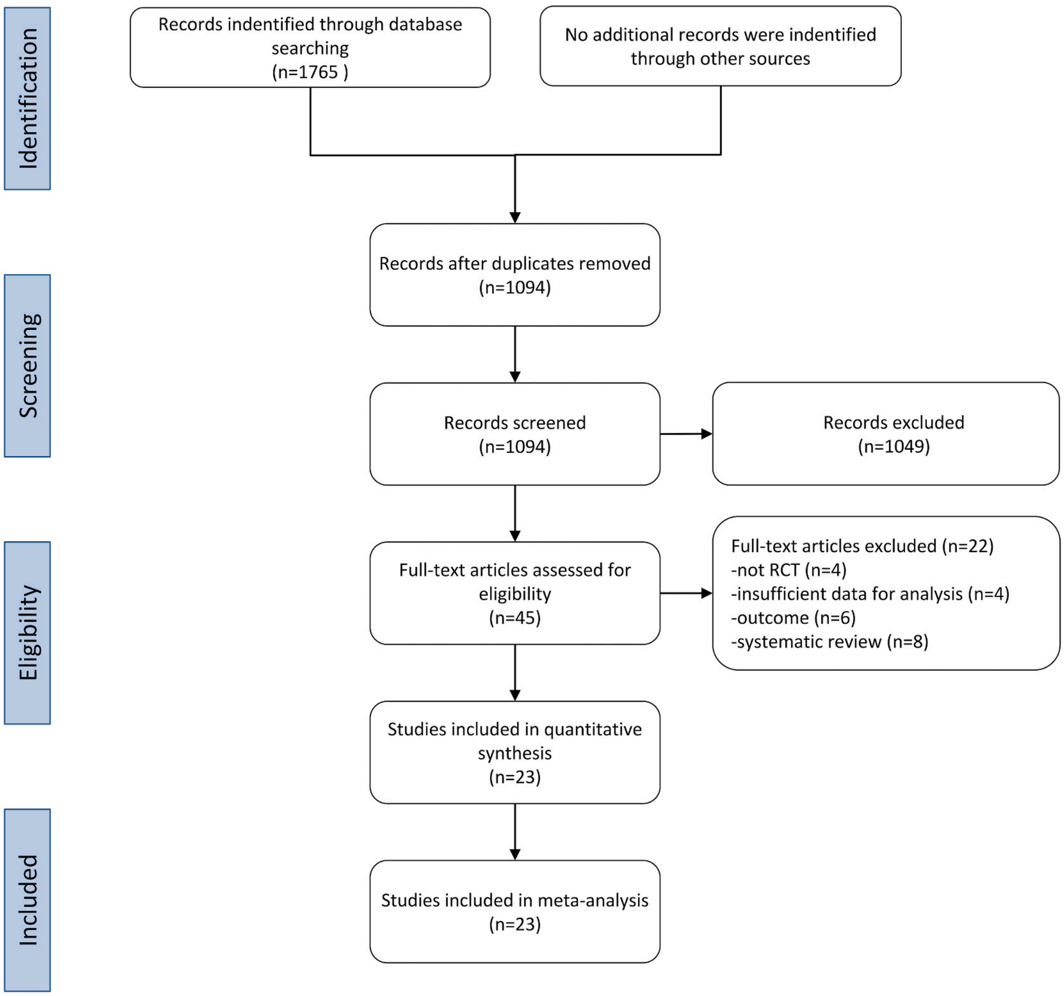


Fig. 1. Flow diagram of study search and selection.

Table 1
Details from included studies.

Study ID	Sample (T/C)	Disease	Age	Gender (M/F)	Intervention (T/C)	Stimulation time	number of sessions	Outcomes
Jobst 1986 [14]	12/12	COPD	T: 67.4 ± 11.3; C: 61.5 ± 17.6	NR	A/SA	NR	13	Mod Borg; SOB; BP; 6MWD
Kuhlemann 1997 [34]	4/6	COPD	64.3 ± 10.4	7/3	A + BT/SA + BT	NR	14	CRQ; BP
Biernacki 1998 [37]	23*	Asthma	63 ± 15	10/13	A + BT/SA + BT	20 min	1	BP
Medici 2002 [44]	23/23	Asthma	T: 39.3 ± 11.4; C: 38.4 ± 11.8	21/25	A/SA	20 min	16	BP; AR
Shapira 2002 [41]	23*	Asthma	NR	NR	A + BT/SA + BT	20–30 min	4	BP
Maa 2003 [40]	11/13	Asthma	<65 y: 8 ≥65 y: 16	16/8	A + BT/BT	30 min	20	Mod Borg; VAS; SGRQ; 6MWD; AR
Jia J 2004 [33]	22/22	COPD	NR	NR	A + PR/PR	30 min	NR	BP
Lewith 2004 [35]	32*	COPD	66.6 ± 13.4	NR	A/SA	20 min	6	VAS; SGRQ; AR
Zhang WP 2006 [43]	40/31	Asthma	T: 47.1 ± 13.1; C: 45.2 ± 14.6	19/52	A + BT/BT	30 min	10	BP
Chu 2007 [39]	18*	Asthma	63 ± 11	12/6	A/SA	15–30 min	1	BP
Choi 2010 [38]	15/15	Asthma	T: 48.27 ± 7.99; C: 57.4 ± 7.67	13/17	A/SA	10 min	12	BP; AR
Deering 2011 [29]	16/25	COPD	T: 65.1 ± 9.7; C: 67.7 ± 5.3	NR	A + PR/PR	20 min	7	Borg; mMRC; BP; SGRQ
Suzuki 2012 [13]	34/34	COPD	T: 72.7 ± 6.8; C: 72.5 ± 7.4	63/5	A + BT/SA + BT	50 min	12	Borg; BP; 6MWD; SGRQ; AR
Tan C 2012 [42]	31/10	Asthma	T: 29–70; C: 32-59	12/29	A + WM/WM	30 min	36	AQLQ; AR
Tong J 2014 [36]	16/14	COPD	T: 64 ± 6; C: 67 ± 6	27/3	EA + AE/SA + AE	30 min	10–15	BP; 6MWD; SGRQ
Feng 2016 [30]	36/36	COPD	T: 67.8 ± 5.4; C: 67.1 ± 6.1	64/8	A + BT/SA + BT	30 min	24	Borg; BP; 6MWD; SGRQ; AR
Cheng 2017 [45]	14/14	Lung cancer	T: 58 ± 5.2; C: 62 ± 4.3	13/15	A + BT/SA + BT	45 min	8	FACT-LCS
Ge Y 2017 [31]	24/20	COPD	T: 65 ± 6; C: 65 ± 7	38/6	EA + AE/SA + AE	30 min	14	BP; 6MWD
Li 2019 [15]	45/46	COPD	T: 65.9 ± 11.1; C: 67.0 ± 1.0	58/33	A + BT/SA + BT	30 min	18	Borg; BP; 6MWD; AR
Wang YL 2019 [47]	93/47	Lung cancer	T: 53 ± 6/55 ± 7; C: 53 ± 7	87/53	A + WM/WM	30 min	3	KPS; AR
Kong 2020 [46]	10/10	Lung cancer	T: 65 (52.2–77.7); C: 69.9 (62–83.1)	15/5	A + RT/RT	15 min	12	Borg; BP; 6MWD; AR
He Y 2021 [32]	30/26	COPD	T: 65 ± 6; C: 65 ± 7	50/6	EA + AE/SA + AE	30 min	14	BP; 6MWD; mMRC; CAT
Song 2022 [48]	61/61	Lung cancer	T: 64.02 ± 3.57; C: 64.18 ± 3.71	84/38	A + RT/RT	25–30 min	1	KPS; AR

A: acupuncture; AE: aerobic exercise; AR: adverse reaction; BP: breathing physiology; BT: basic treatment; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; CRQ: chronic respiratory questionnaire; EA: electroacupuncture; FACT-LCS: Functional Assessment of Cancer Therapy-Lung Cancer Subscale; KPS: karnofsky performance status; mMRC: modified Medical Research Council scale; Mod Borg: modified Borg test score; PR: pulmonary rehabilitation; RT: radiotherapy; SA: sham acupuncture; SGRQ: St. George's Respiratory Questionnaire; SOB: shortness of breath; VAS: visual analogue scale; WM: western medicine; 6-MWD: 6-min walking distance; * indicate cross-over study.

Most studies used five to ten acupoints, and only three used fewer than four points [35,37,47]. Zusanli (ST36) (in twelve trials), Feishu (BL13) (in eleven trials), Taixi (KI3) (in eight trials) and Hegu (LI4) (in seven trials) were the most frequently used acupuncture points. Study duration varied from seven days to twelve weeks, with treatment frequency ranging from daily to weekly. The majority of trials evaluated all results at the conclusion of the intervention, with seven trials including follow-up periods ranging from two weeks to six months.

3.3. Risk of bias of included studies and GRADE

A thorough evaluation of the potential for bias in the studies that were included is outlined in Fig. 2. The risk of bias was assessed

Table 2
Key acupoints and treatment regimen of included studies.

Study ID	Key acupoints	Treatment regimen	Follow-up
Jobst 1986 [14]	Points according to the principles of traditional Chinese medicine	13 sessions over 3 weeks	No follow-up
Kuhlemann 1997 [34]	LU1, LU9, BL13, KI3, BL23, ST36, ST40, SP6, CV17, CV6	7 sessions in 14 days: every 2 days	No follow-up
Biernacki 1998 [37]	CV17	1 session	2 weeks
Medici 2002 [44]	DU14, EX-B1, BL13, KI3, LU10, SP6, LI4, LI11, ST36, LR13, PC6	Twice weekly for 8 weeks	6 months
Shapira 2002 [41]	Points according to the principles of traditional Chinese medicine	4 sessions in a week	No follow-up
Maa 2003 [40]	LU1, PC6, ST36, DU14, EX-B1	3 times weekly for 10 sessions, followed by 1 week without treatment, and then 3 times weekly for another 10 sessions	No follow-up
Jia J 2004 [33]	Major acupoints: BL13, BL43, BL23, ST36, KI3, LU9 + 1–2 matching acupoints: EX-B1, CV17, LU5, LU7	50 sessions: every 2 days for 100 days	No follow-up
Lewith 2004 [35]	LI4	Twice a week for 3 weeks	No follow-up
Zhang WP 2007 [43]	LI11, LU7, LU1, PC6, ST36, SP6, KI3	Once a day for 10 days	No follow-up
Chu 2007 [39]	LU7, LI4, PC6, ST40, LI11, PC3	1 session	No follow-up
Choi 2010 [38]	CV22 and bilateral LU5, ST40, BL13, EX-B1	3 times a week for 4 weeks	2 weeks
Deering 2011 [29]	LI11, LI10, SJ10, SJ6, LU5, LU7	Once a week for 7 weeks	3 months
Suzuki 2012 [13]	LU1, LU9, LI18, CV4, CV12, ST36, KI3, GB12, BL13, BL20 and BL23	Once a week for 12 weeks	No follow-up
Tan C 2012 [42]	LU5, LU6, LU7, BL13, LI11, LI4, ST25, ST37	3 times a week for 12 weeks	No follow-up
Tong J 2014 [36]	CV17, ST18, CV4, CV12, ST25, ST16, Unilateral LI4, ST40	10-15 sessions: 2 to 3 times a week for 5 weeks	No follow-up
Feng 2016 [30]	LU1, LU9, LI18, ST36, GB12, BL13, BL20, and BL23	3 times a week for 8 weeks	No follow-up
Cheng 2017 [45]	LI4, Ren-6, ST36, KI3, SP6	Twice per week for 4 weeks	2 weeks
Ge Y 2017 [31]	CV17, ST18, CV4, CV12, ST25	14 sessions: 2 to 3 times per week	No follow-up
Li 2019 [15]	ST36, BL20, BL13, EX-B1	3 times weekly for 6 weeks	No follow-up
Wang YL 2019 [47]	ST36, RN12, PC6	Once a day for 3 days	No follow-up
Kong 2020 [46]	LR3, LI4, LU1, LU2, LU9, BL13, BL20, BL23, ST36, KI3, GB12, PC6, GV14, CV4, CV12	twice per week for 6 weeks	2 weeks
He Y 2021 [32]	CV17, ST18, CV4, CV12, ST25, ST16	3 times a week for 14 times	No follow-up
Song 2022 [48]	ST36, GB39, BL11, SP10, KI3, BL13, LR8, BL15, SI3	1 session	4 weeks

based on dyspnea and breathing physiology lung function in 8 [13–15,29,30,35,40,46] and 12 studies [31–34,36–39,41,43,44,46], respectively. The risk of bias in three studies was related to the occurrence of adverse events [42,47,48]. Three study outcomes were rated as having low overall bias. The other study outcomes were rated with some concerns. Among 23 RCTs, 9 had low risk of bias from randomization, 15 had low risk of bias from deviation in intervention, 22 had low risk of bias from missing outcome data, all 23 had low risk of bias in outcome measurement, and 8 had low risk of selection bias. According to the RoB 2 assessment algorithm, three study outcomes were deemed to have a low risk of bias, while the remaining study outcomes were assessed with some concerns.

Table 3 summarized that the evidence from the studies analyzed was rated as moderate, low, or very low according to GRADE, mainly because of some serious risks of bias, inconsistency in effect estimates and imprecision, as the small sample sizes caused wide confidence intervals. Therefore, the findings interpreted with caution.

3.4. Outcomes

3.4.1. Dyspnea

A total of nine trials reported dyspnea severity [13–15,29,30,32,35,40,46]. Borg scale score was used in eight studies, VAS score was used in one study [35], and mMRC scale was used in one study [32]. Considering that the scoring method of mMRC was different from Borg and VAS, the study evaluated by mMRC was not included in the analysis. The meta-analysis of eight trials involving 375 patients showed a statistically significant effect favoring the acupuncture group (MD = −2.25; 95 % CI: −3.46, −1.03; $P = 0.0003$). High heterogeneity presented among studies ($I^2 = 89$ %, $P < 0.00001$) (Fig. 3).

The subgroup analysis including only sham controlled studies (n = 199) yielded consistent results. These four studies [13,14,30,35] that included sham control groups and lasted for a minimum of three weeks showed a notable improvement in breathing difficulty

Fig. 2. Risk of bias summary. Red sign: high risk of bias; Green sign: low risk of bias; Yellow sign: some concerns. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(MD = −3.57, 95 % CI: −4.42, −2.72; $P < 0.00001$) and not significant heterogeneity ($I^2 = 18$ %, $P = 0.30$) (Supplementary Fig. S1). Based on the result of the subgroup analysis for different diseases, acupuncture was found to be as effective as the pooled analysis (Supplementary Fig. S2).

3.4.2. Breathing physiology

Lung function was assessed in 17 trials using FEV_1, FVC, or FEV_1% predicted. For FEV_1, six studies [13–15,37–39] were meta-analyzed which showed no significant improvement in acupuncture group (MD = 0.04; 95 % CI: −0.04, 0.13; $P = 0.34$) and no heterogeneity detected ($I^2 = 0$ %, $P = 0.67$) (Fig. 4A). In five trials [13–15,30,37], there was no notable variation between groups in terms of FVC (MD = 0.11; 95 % CI: −0.04, 0.26; $P = 0.15$) and no heterogeneity was found ($I^2 = 0$ %, $P = 0.78$) (Fig. 4B). A total of 14 studies reported FEV_1% predicted. The acupuncture group showed enhanced FEV_1% predicted in comparison to the control group, with a mean difference of 4.64 (95 % CI: 2.24, 7.04; $P = 0.0001$) and moderate heterogeneity ($I^2 = 41$ %, $P = 0.05$) (Fig. 4C). The above results were consistent when the comparator was sham acupuncture (Supplementary Figs. S3, S5, and S7). In addition, consistent results were also found in subgroup analyses of different diseases and types of acupuncture (Supplementary Figs. S4, S6, S8 and S9). Manual and electroacupuncture both improved FEV_1% predicted.

3.4.3. Exercise capacity

Nine RCTs [13–15,30–32,36,40,46] including 413 patients assessed exercise capacity using the 6MWD. The meta-analysis showed a significant improvement of 52.39 m in the 6MWD for the acupuncture group compared to the control group (MD = 52.39; 95 % CI: 29.38, 75.41; $P < 0.00001$) with low heterogeneity ($I^2 = 42$ %, $P = 0.09$) (Fig. 5). The subgroup analysis including only sham acupuncture yielded a consistent result with the pooled analysis (Supplementary Fig. S10). Subgroup analyses of different diseases and types of acupuncture also showed consistent results (Supplementary Figs. S11 and S12).

3.4.4. Quality of life

Quality of life was reported in eight studies. Six studies [13,29,30,35,36,40] involving 270 patients reported the SGRQ. The pooled analysis showed a statistically significant improvement in SGRQ in acupuncture treatment group (MD = −5.42; 95 % CI: −10.46, −0.39; $P = 0.03$) with moderate heterogeneity ($I^2 = 56$ %, $P = 0.05$) (Fig. 6A). Additionally, a significant result was also revealed in the subgroup analysis of sham control (Supplementary Fig. S13). The subgroup analysis according to different diseases yielded a

Table 3
Summary of findings for main comparisons.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comparison	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Dyspnea (assessed with: Borg scale and VAS scale)												
8	RCTs	serious[a]	serious[b]	not serious	serious[c]	not serious	181	194	–	MD **2.25 lower**(3.46 lower to 1.03 lower)	⨁◯◯◯ Very low	CRITICAL
Breathing physiology (assessed with: FEV1)												
6	RCTs	serious[a]	not serious	not serious	not serious	not serious	141	144	–	MD **0.04 higher** (0.04 lower to 0.13 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Breathing physiology (assessed with: FVC)												
5	RCTs	serious[a]	not serious	not serious	not serious	not serious	143	145	–	MD **0.11 higher** (0.04 lower to 0.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Breathing physiology (assessed with: FEV1% predicted)												
14	RCTs	serious[a]	not serious	not serious	serious[c]	not serious	326	321	–	MD **4.64 higher** (2.24 higher to 7.04 higher)	⨁⨁◯◯ Low	CRITICAL
Exercise capacity (assessed with: 6MWD)												
9	RCTs	serious[a]	not serious	not serious	not serious[c]	not serious	209	204	–	MD **52.39 higher** (29.38 higher to 75.41 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Quality of life (assessed with: SGRQ)												
6	RCTs	serious[a]	serious[b]	not serious	not serious	not serious	130	140	–	MD **5.42 lower** (10.46 lower to 0.39 lower)	⨁⨁◯◯ Low	IMPORTANT
Quality of life (assessed with: KPS)												
2	RCTs	serious[a]	serious[b]	not serious	not serious	not serious	154	108	–	MD **8.9 higher** (5.07 higher to 12.73 higher)	⨁⨁◯◯ Low	IMPORTANT
Adverse events												
10	RCTs	serious[a]	serious[b]	not serious	not serious	not serious	33/347 (9.5 %)	12/283 (4.2 %)	**RR 2.14** (1.22–3.75)	**48 more per 1000** (from 9 more to 117 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; RCTs, randomized controlled trials. *GRADE Working Group grades of evidence High quality:* We are very confident that the true effect lies close to the estimated effect. *Moderate quality:* We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low quality:* Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimated effect. *Very low quality:* We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimated effect. a. Downgraded by 1 level due to risk of bias; most included studies were rated as having 'some concerns' on RoB2 regarding risk of bias. b. Downgraded by 1 level due to inconsistency; heterogeneity was observed in the analysis. c. Downgraded by 1 level due to imprecision; confidence intervals could not rule out the possibility of no effect (crosses null). ⨁⨁⨁⨁High quality: We are very confident that the true effect lies close to the estimated effect. ⨁⨁⨁◯Moderate quality: We are moderately confident in the effect estimate. ⨁⨁◯◯Low quality: Our confidence in the effect estimate is limited. ⨁◯◯◯Very low quality: We have very little confidence in the effect estimate.

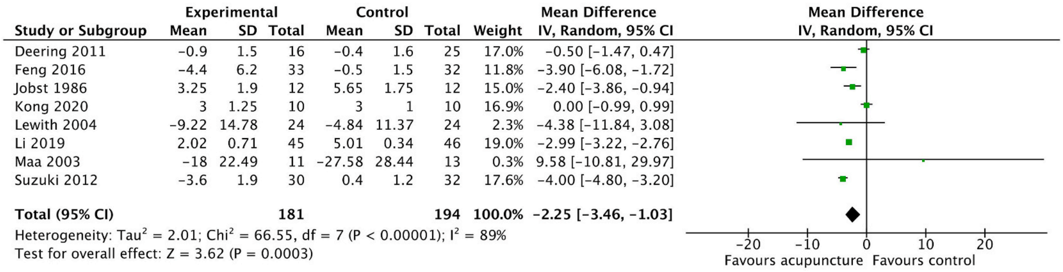


Fig. 3. Forest plot of dyspnea.

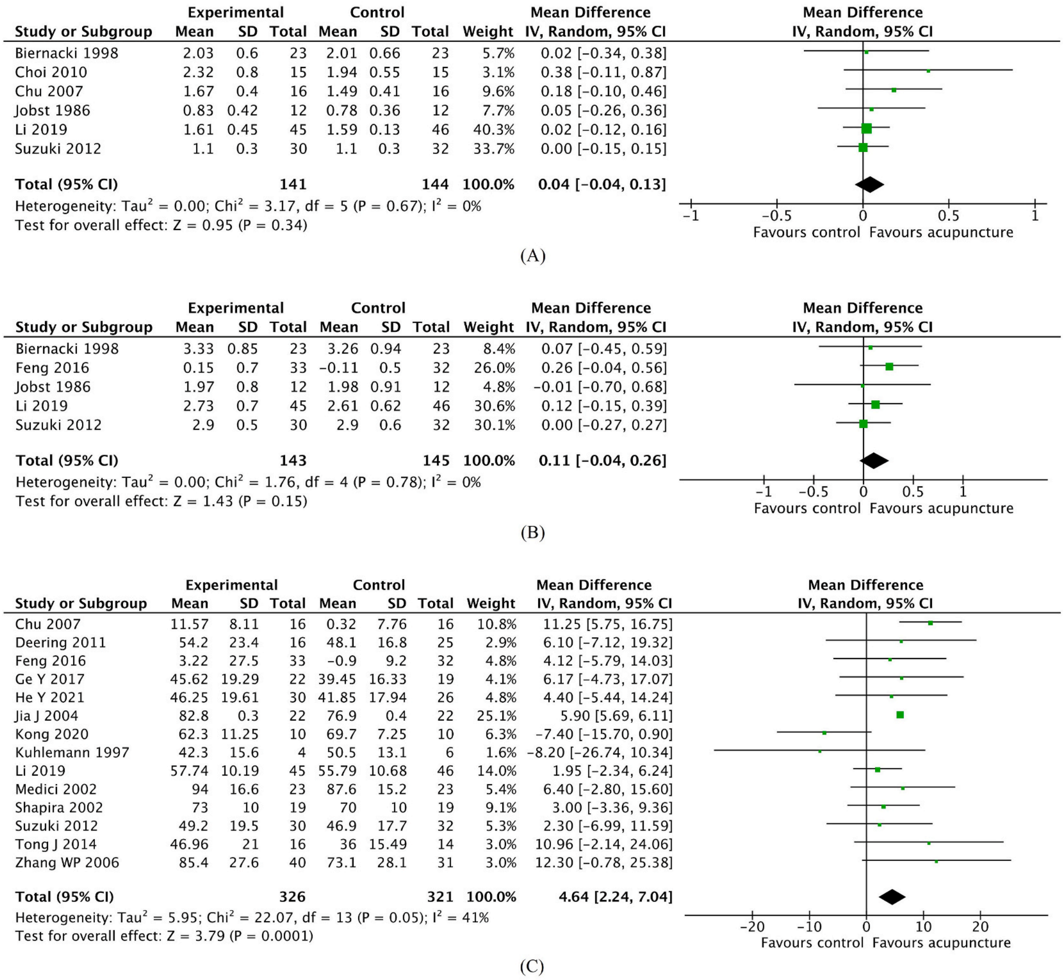


Fig. 4. Forest plot of breathing physiology. (A) Forest plot of FEV_1. (B) Forest plot of FVC. (C) Forest plot of FEV_1% predicted.

consistent result with the pooled analysis (Supplementary Fig. S14).

Two studies involving 262 patients repoted KPS [43,48]. The acupuncture group had improved KPS compared with the control group (MD = 8.9; 95 % CI: 5.07, 12.73; $P < 0.00001$) with moderate heterogeneity ($I^2 = 51$ %, $P = 0.15$) (Fig. 6B).

3.4.5. Adverse events

Adverse events of acupuncture treatment were reported in ten trials [13,15,35,38,40,42,44,46–48]. Meta-analysis showed moderate heterogeneity in results ($I^2 = 57$ %, $P = 0.01$) with no significant adverse outcomes observed in either group (RD = 0.05; 95 % CI, −0.0, 0.1; $P = 0.07$) (Fig. 7), which indicated that acupuncture is a secure and well-tolerated technique. None of the severe advere effects was reported in all study subjects. The subgroup analysis including sham controlled studies yielded consistent results

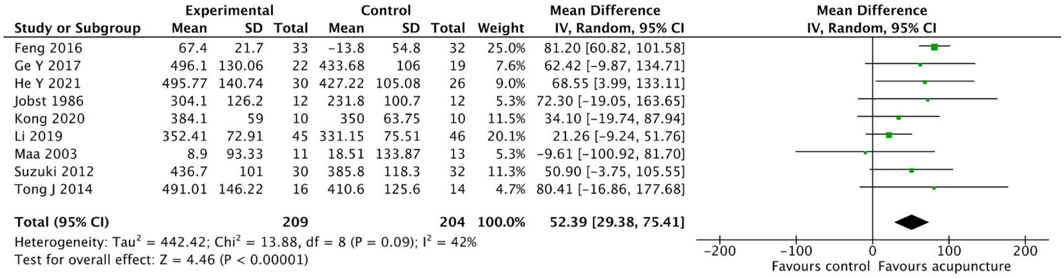
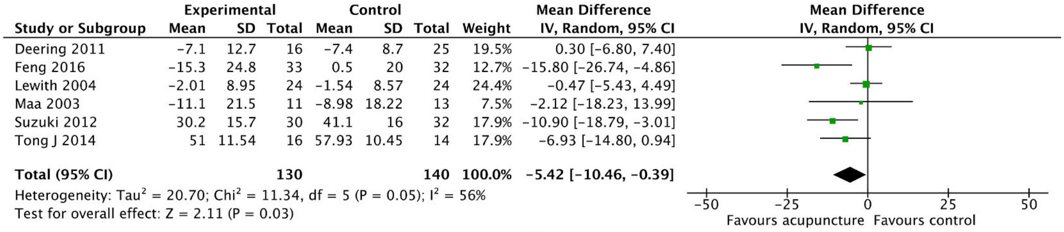
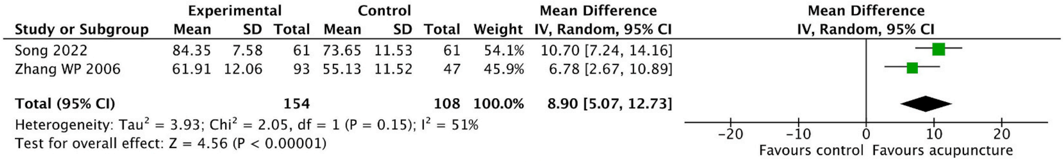


Fig. 5. Forest plot of 6MWD.



(A)



(B)

Fig. 6. Forest plot of quality of life. (A) Forest plot of SGRQ. (B) Forest plot of KPS.

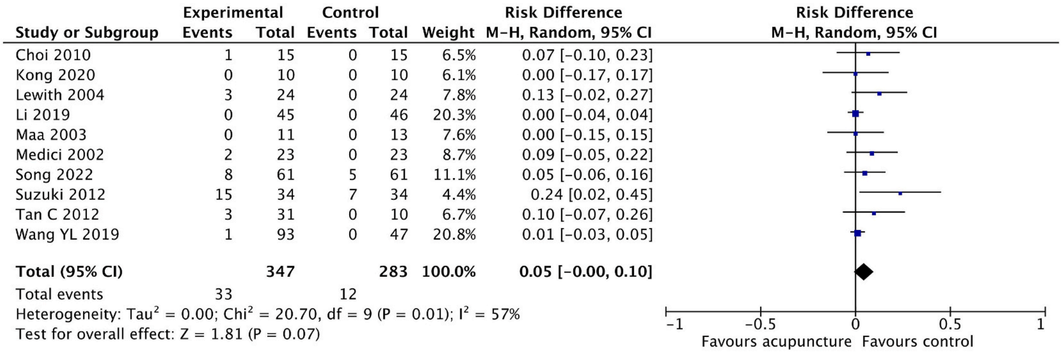


Fig. 7. Forest plot of adverse events.

(Supplementary Fig. S15). In the subgroup analysis according to different diseases, COPD, asthma and lung cancer group yielded consistent results (Supplementary Fig. S16).

3.5. Publication bias

Funnel plot was constructed to assess publication bias when there were ≥7 studies included in the meta-analysis. As shown in Fig. 8, the funnel plot of dyspnea, FEV_1% predicted and 6MWD were symmetric in visual conditions. No evidence of publication bias was found.

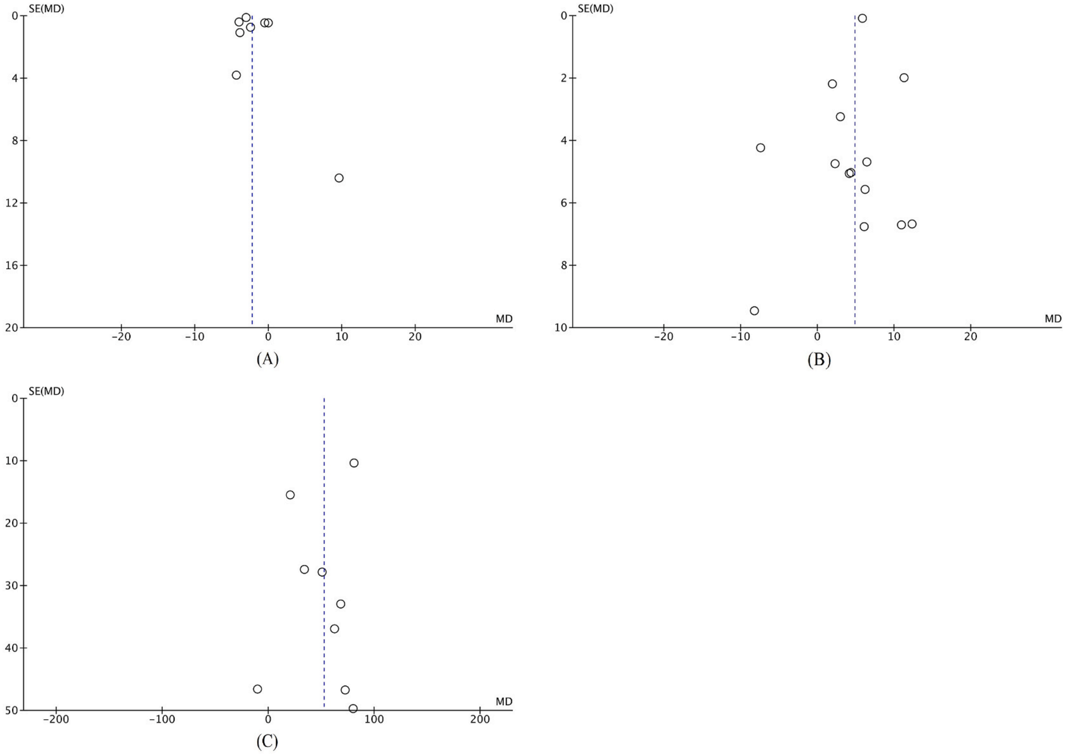


Fig. 8. Funnel plot. (A) Funnel plot of dyspnea. (B) Funnel plot of FEV_1% predicted. (C) Funnel plot of 6MWD.

4. Discussion

4.1. Summary of main results

To our knowledge, this was the first meta-analysis and systematic review that evaluates acupuncture for dyspnea and breathing physiology in CRDs. Twenty-three studies assessing the therapeutic effect of acupuncture were included in this meta-analysis. Benefits of acupuncture were observed for CRDs patients with regard to dyspnea, quality of life and exercise capacity compared with control (sham acupuncture and no acupuncture). Those benefits were consistent when the comparator was sham acupuncture. Moreover, consistent results were found in subgroup analyses based on different diseases and types of acupuncture. For breathing physiology, acupuncture could not improve FEV_1 and FVC. Acupuncture treatment protocols varied widely with different acupuncture points, variable treatment regimens, and diverse treatment durations.

4.2. Dyspnea

Dyspnea is a common symptom universally present in patients suffering from CRDs. Although therapies including inhaled bronchodilators, pulmonary rehabilitation even opiates have been used in different diseases, certain patients still have refractory dyspnea despite on maximum treatments. The development of effective therapy for dyspnea is highly great based on its relation with quality of life, exercise tolerance and mortality. This meta-analysis firstly showed a beneficial effect of acupuncture on patients CRDs including COPD, lung cancer and asthma. We observed that most included trials evaluated dyspnea in CRDs by using Borg scale scores or VAS. It appeared that the Borg sacles and VAS were the best subjective measures of dyspnea and there was a good correlation between them [49,50]. Additionally, they were also used for assessing dyspnea in different types of chronic diseases in previous studies [17,40,51]. Therefore, we believed that it was reasonbale to evaluate dyspnea using the two indexes across all CRDs in the meta-analysis. Although with the exception of COPD, asthma and lung cancer, other studies of CRDs meeting the inclusion criter were not retrieved, e.g. interstitial lung disease, these diseases were also worth researching in the future.

While the exact methods of acupuncture for treating CRDs with dyspnea are not fully understood, a set of discoveries offer the theoretical and mechanistic foundation for the effectiveness of acupuncture in alleviating dyspnea. Firstly, studies suggested that central nerves regulating pain and dyspnea probably overlapped [52,53]. A meta-analysis that focused on brain responses by functional magnetic resonance imaging following acupuncture needle stimulation detected activation in the sensorimotor cortical network, including the insula, thalamus and anterior cingulate cortex, and deactivation in the limbic-paralimbic neocortical network, including the medial prefrontal cortex, caudate, amygdala, and parahippocampus [54]. Improvement of dyspnea by acupuncture might be associated with its effects on the activated cerebral regions, as was thought to occur when it was used for pain relief. Secondly, acupuncture could potentially have a neuro-endocrine regulatory function through stimulation of the vagus nerve and reduction of acetylcholine release in the lungs, resulting in bronchodilating and anti-inflammatory effects [55]. Thirdly, acupuncture may have a positive impact by increasing levels of β-endorphin, a natural pain-relieving chemical that helps with dyspnea and pain in COPD patients [25,56]. Furthermore, acupuncture could alleviate shortness of breath by reducing feelings of depression and anxiety [57,58]. Mechanisms related to the effect of acupuncture on dyspnea, and clinical questions such as which type of dyspnea, e.g. air hunger, chest tightness, and respiratory work/effort, is targeted for acupuncture need to be further answered [4].

4.3. Breathing physiology

Inconsistent results were found in terms of the effect of acupuncture on lung function in our study. No benefit was identified for acupuncture on FEV_1 and FVC, which supported by the findings of Jobst [14], Suzuki [13], Coyle et al. [59], whereas acupuncture could improve FEV_1% predicted. The reason for the inconsistencies may be largely due to the different studies included in analyses. We did not include FEV_1/FVC as one of the outcomes due to the fact that it is a criterion for diagnosing airflow obstruction, which is commonly used as an diagnostic criterion of COPD. Nevertheless, it lacked the necessary sensitivity and specificity for accurate diagnosis in conditions like asthma [60], and was not employed to assess the extent of lung function impairment in clinical settings. FEV_1% predicted is calculated by dividing a patient's FEV_1 index by the average FEV_1 of a comparable population with similar gender, age, and characteristics. Using reference equations can cause challenges when applying and understanding this data in both individuals and research groups, as reference equations vary among labs and studies, resulting in different categorizations for individuals with similar lung function based on the equations used [61]. Furthermore, the utilization of percent predicted for categorizing the extent of lung function decline could result in varying evaluations of severity among different racial and gender groups [62]. Miller and Pedersen discovered that the absolute FEV_1 were a more accurate indicator of survival compared to the percent predicted FEV_1 [63]. In the context of CRDs, using absolute value of FEV_1 and FVC for the assessment of breathing physiology was more suitable across different diseases. In addition, most multicenters RCTs of asthma and COPD with large sample size such as the TORCH, UPLIFT® and SYGMA studies assessed the absolute value of FEV_1 and FVC for treatment effects [64–66]. Therefore, we believe absolute value of FEV_1 and FVC were beter indicators of breathing physiology in CRDs. It is noted that studies with FEV_1% predicted as outcome did not report absolute value of FEV_1 and FVC which was precluded from a comparison., the pooled analyses showed that acupuncture did not improve breathing physiology in terms of FEV_1 and FVC in patients with CRDs. Nevertheless, considering current evidence, the effectiveness of acupuncture on breathing physiology still requires further investigation through robust clinical trials involving a significant number of participants.

4.4. QoL and exercise capacity

This study showed that acupuncture could be effective in improving QoL in CRDs patients, and this could be partially explained by a better perception of dyspnea. The majority of studies utilized the 6MWD to assess exercise capacity, which measured the ability to sustain regular physical activity. The acupuncture group showed a notable enhancement in this aspect. Research has shown that acupuncture may enhance the 6MWD by decreasing tension in the muscles used for breathing and boosting oxygen levels [13,67], which could also be associated with the improvement in dyspnea. This study addressed the safety of acupuncture by noting similar adverse events in both groups; however, the reporting of this outcome was really limited.

4.5. Acupoint selection

Although the acupoints used in the 23 RCTs varied, here are the eight most commonly used points: Zusanli (ST36), Feishu (BL13), Hegu (LI4), Taixi (KI3), Zhongfu (LU1), Shanzhong (CV17), Dingchuan (EX-B1) and Shenshu (BL23). Based on TCM principles, these acupoints were primarily associated with meridians of lung and kidney. The theory of TCM proposes that dyspnea is closely associated with lung and kidney disorders, and dyspnea can be treated by regulating the lung and strengthening the kidney. Feishu (BL13) are the Back-Shu acupoints of the lung, which has the effect of regulating and tonifying lung *Qi*. Zhongfu (LU1), and Shanzhong (CV17) could modulate and benefit the functions of lung *Qi*. Dingchuan (EX-B1) does not belong to a standard meridian, but has a specific effect which is the alleviation of dyspnea. Zusanli (ST36) could supplement *Qi* and blood. The combination of Shenshu (BL23) and Zusanli (ST36) could reinforcing the congenital kidney *Qi* by tonifying *Qi* and reinforcing blood. As the Yuan-Source acupoint of the kidney meridian, Taixi (KI3) is capable of nourishing kidney yin and warming kidney yang. Combining Shenshu (BL23) and Taixi (KI3) could replenish the kidney essence. Hegu (LI4) could activate blood circulation and make meridians unobstructed. Hence, the above eight acupoints could regulate the lung and reinforce the kidney, thus benefiting CRDs patients with dyspnea.

4.6. Heterogeneity

It is of note that high heterogeneity was detected in the dyspnea data. Any inconsistency across individual studies, including the size of trials, the difference of the intervention, the assessment of outcomes, might lead to heterogeneity, which was a common and inevitable problem. Based on the subgroup analysis, heterogeneity was low in sham acupuncture subgroup (*I2*: 18 vs. 92 %), indicating that comparator of study might be one source of heterogeneity and sham acupuncture might be a more reliable control for RCTs compared with no acupuncture. However, the pooled analyses including all controls yielded a significant result that aligned with the subgroup assessment of sham acupuncture, suggesting that heterogeneity might not have an impact on our final result.

4.7. Agreements and disagreements with other studies or reviews

Previously, two meta-analyses addressing similar topics were published in 2019 and 2020 [17,68], but there were some differences that made this current review necessary. Firstly, for included patients, we searched all types of CRDs, and COPD, lung cancer and asthma were included for assessing the primary outcomes, while Fernández-Jané et al. focused on COPD only and von Trott et al. included advanced diseases including COPD (stable stage and acute exacerbations), lung cancer and breast cancer. In addition, we conducted analyses for other important outcomes that are closely related to dyspnea and also with clinical significance such as breathing physiology, which was absent in von Trott's. Finally, warm needle acupuncture included in Fernández-Jané's meta-analysis was excluded in our study, for combination with moxibustion might obscure the effect of acupuncture. For Fernández-Jané et al., no difference and statistical benefit were seen for dyspnea when acupuncture was compared with no acupuncture and sham acupuncture, respectively. The reason for the inconsistencies might be the smaller sample size, single disease of COPD, different inclusion criteria and different subgroups in their analyses. von Trott et al. found significant beneficial effects of acupuncture on breathlessness severity, exercise tolerance in advanced diseases, which were consistent with our study. Our review showed a significant improvement in breathlessness in CRDs, which strengthened the efficiency of acupuncture.

4.8. Limitations of study

It is important to acknowledge the various constraints of our meta-analysis. Firstly, considering the integrity and comprehensiveness of data, four cross-over studies were included, which might cause heterogeneity for the inconsistency of study design. However, pooling together cross-studies was also a common approach used in previous systematic review [17]. Secondly, we only included Chinese trials from MEDLINE database and other Chinese databases were not included, which might cause publication bias. Although the MEDLINE database is known for its coverage of high-quality studies, the search was not comprehensive enough and there was possibility to miss important studies by not searching Chinese databases or specialised databases.

5. Conclusion

In CRDs patients, acupuncture is a safe therapy that significantly reduced dyspnea, improved QoL and exercise capacity with tolerability in CRDs, whereas no benefit was found for breathing physiology in terms of FEV_1 and FVC. Results were consistent when the comparator was sham acupuncture. In conclusion, acupuncture can be considered an effective non-pharmacological complementary intervention which is potentially for CRDs patients with dyspnea. Given the uneven quality of studies and some controversies, research with high quality and large sample sizes identifying effects of acupuncture is needed for further investigation.

Ethics statement

Ethics committee approval and informed consent were not required for this study because all analyses were based on previous published studies.

Consent to participate

The authors declare their consent to participate in this article.

Consent to publish

The authors declare their consent to publish this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

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CRediT authorship contribution statement

Yan Yu: Writing – original draft, Software, Data curation. **Wei Xiao:** Software, Data curation. **Long-Yi Du:** Methodology, Data curation. **Yu Li:** Investigation, Data curation. **Chan Xiong:** Investigation, Data curation. **Fan-Rong Liang:** Validation, Methodology. **Bing Mao:** Validation, Supervision, Methodology. **Juan-Juan Fu:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31176.

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