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Filiform needle acupuncture for copd: A systematic review and meta- analysis

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ABSTRACT

Background: This is the first part of a larger spectrum systematic review which aims to identify and evaluates the effectiveness of all different non-pharmacological acupuncture techniques used for COPD. In this first publication, we describe the results of filiform needle acupuncture

Methods: Randomised controlled trials up to May 2019 were searched in 11 databases. Data extraction and risk of bias assessment was conducted in pairs independently. RevMan 5.3 was used for the meta-analysis.

Results: 28 trials using filiform needle alone or in combination of other techniques were included. Compared with no acupuncture, no difference was seen for dyspnoea, but statistical benefits were found on quality of life (Std. MD: -0.62, 95%CI: -0.90, -0.34), exercise capacity (stable subgroup) (6MWT MD: 33.05 m, 95%CI: 19.11, 46.99) and lung function (FEV_1% MD: 1.58, 95%CI: 0.51, 2.66). Compared with sham, statistical benefits were found on dyspnoea (Std. MD: -1.07, 95%CI: -1.58, -0.56), quality of life (Std. MD: -0.81, 95%CI: -1.12, -0.49), exercise capacity (6MWT MD: 76.68 m, 95% CI: 39.93, 113.43) and lung function (FEV_1% MD: 5.40, 95%CI: 2.90, 7.91; FEV1/FVC MD: 6.64, 95%CI: 3.44, 9.83).

Conclusions: Results show that filiform needle acupuncture might be beneficial for COPD, but due to the low quality of the studies this should be confirmed by future well-designed trials.

Protocol registration: PROSPERO (identifier: CRD42014015074).

Keywords: COPD Acupuncture therapy Dyspnea Quality of life Systematic review Meta-analysis

1. Background

Chronic obstructive pulmonary disease (COPD) is defined as chronic and irreversible airflow obstruction, characterised by decreased forced expiratory volume in the first second (FEV_1) compared to forced vital capacity (FVC).[1] The main cause of this disease is considered to be smoking or exposure to other gases and harmful particles that cause an inflammatory reaction in the airways and lung parenchyma and structural abnormalities in the airways.[1,2] These alterations trigger the main symptoms of the disease: progressive dyspnoea, chronic cough, sputum production and recurrent respiratory infections that cause exacerbations of the disease.[1] An increase in the people affected by COPD is expected in the coming years, and it is estimated that COPD will be the fourth most prevalent disease worldwide in 2030.[3]

Treatment of COPD is symptomatic; there is no intervention able to modify the progressive decline in lung function in the long term.[2] Consequently, the aim of all interventions is to reduce its symptoms and improve quality of life as long as possible.

Acupuncture is a therapy that derives from the Traditional Chinese Medicine (TCM) based on the stimulation of specific areas of the body surface (acupuncture points) using different stimuli such as the insertion of acupuncture needles (filiform needles), application of pressure (acupressure), heat (moxibustion) or electricity (electroacupuncture).[4] Some studies have been published indicating that acupuncture may have beneficial effects on COPD patients with regard to dyspnoea, exercise capacity, quality of life and lung function.[5–8] Barring these results, at the time this review was designed, there was only one specific systematic review on the effect of acupuncture and its potential use in the treatment of COPD.[9] This review, which included 16 studies, concluded that acupuncture was beneficial in outcomes like dyspnoea, exercise capacity and quality of life but not on lung function. However, this review pooled together different acupuncture techniques like filiform needle, moxibustion and acupoint transcutaneous electrical nerve stimulation and acupressure as well as pharmacological modalities such as point application therapy. When authors tried to analyse each technique separately, they only had one study per subgroup (except for Acu-TENS).

The aim of our review was to identify and evaluate separately the efficacy of non-pharmacological acupuncture techniques in the treat- ment of COPD patients and, therefore, perform a large spectrum review. Due to the vast amount of data obtained and the impossibility of condensing all of it in one single paper, we finally decided to publish the results in two different papers.

In this first publication, we will only focus in filiform needle acupuncture, alone or in combination with other techniques, due to the fact that it is the most common acupuncture technique used around the world.

2. Methods

2.1. *Protocol and registration*

For this review we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[10] The protocol was previously registered at PROSPERO (CRD42014015074) and is available on: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42014015074

2.2. *Eligibility criteria*

We included randomised controlled trials or quasi-randomised trials and crossover studies, meeting all following criteria[1] performed in COPD patients with different grades of obstruction (GOLD A to D) in exacerbation or stable periods; [2] assessing non-pharmacological modalities of acupuncture (filiform needle, electroacupuncture, acupressure, moxibustion, ear acupuncture, etc.) compared with a control group (sham acupuncture or no acupuncture), in addition to usual care (medication, physiotherapy, pulmonary rehabilitation, etc.); and[3] reporting at least one of the following outcomes: dyspnoea, quality of life, adverse effects, exercise capacity, lung function or anxiety and depression.

Exclusion criteria were as follows[1] if acupuncture was compared with a different acupuncture technique or a therapy not used in usual care; and[2] randomised cluster studies.

Due to do the large amount of different acupuncture techniques found, we decided to exclude those that were mainly used only in China and therefore focus on the most known and practiced ones in the world. Trials about those techniques are listed in the results section but were not analyzed. This exclusion criteria was not contemplated in our original protocol.

No language restriction was applied.

2.3. *Information sources*

An electronic search was performed up until May 2019. Databases included were Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED (Ovid), PEDro, PsycINFO, CNKI, VIP, Wanfang and Sino-Med.
In addition, the bibliographies of selected articles were consulted in search of additional studies not detected in the initial search. Manual reviews of international respiratory disease conferences (European Respiratory Society and American Association for Respiratory Care) were also performed from 2010 to 2019.

2.4. *Search*

We conducted a comprehensive search using the following key words and their variations: “acupuncture”, “moxibustion”, “acupressure”, “electroacupuncture”, “AcuTENS”, “ear acupuncture”, “cupping”, “COPD”, “randomised control trial”. The searching strategy was adjusted for each database (see additional file 1).

2.5. *Study selection*

The reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX, MY, MS and NGT) worked in pairs and independently identified the articles that met the inclusion criteria, first through title and abstract and afterwards through full text paper.

2.6. *Data collection process*

The reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX, MY, MS and NGT) worked in pairs and independently extracted the data using a standardised data extraction form. A pilot test prior to the data extraction was performed to check suitability of the form, as well as its understanding by the reviewers. A third author was consulted in case of discrepancies. Lack of data or inconsistent data were managed by contacting the trial authors; if this was not possible, data was not included in the meta-analysis.

2.7. *Risk of bias in individual studies*

The Cochrane risk of bias assessment tool[11] was used to assess the papers’ risk of bias.

2.8. *Summary measures*

Continuous outcomes were expressed as mean difference (MD) with 95% confidence interval (CI) or standardised mean difference (Std. MD) when different scales were used. For trials with different arms using acupuncture, results were combined before meta-analysis using the Cochrane Handbook.[17]

2.9. *Synthesis of results*

Heterogeneity of the study results was evaluated through the I^2 statistic. For the meta-analysis, post-treatment data from each group or post-treatment differences between groups were used. When this was not reported or large baseline differences between the groups were found, the differences from baseline data from each group were used. The results were combined in a meta-analysis using RevMan 5.3 software and applying a fixed effects model to summarise the results when heterogeneity was not relevant ($I^2 < 30\%$). Otherwise, a random effects model was used. If I^2value was over 70%, a narrative synthesis of the available data was performed.

2.10. *Additional analyses*

Since studies included patients with different conditions and this could lead to heterogeneity in our results, we decided to separate them in two subgroups in all meta-analysis, stable patients and exacerbated patients. Therefore, when heterogeneity was too big ($I^2 > 70\%$) between subgroups or in one of the subgroups, results

are presented separately.

2.11. *Publication bias*

Publication bias was assessed for meta-analysis with more than 10 trials using a funnel plot.

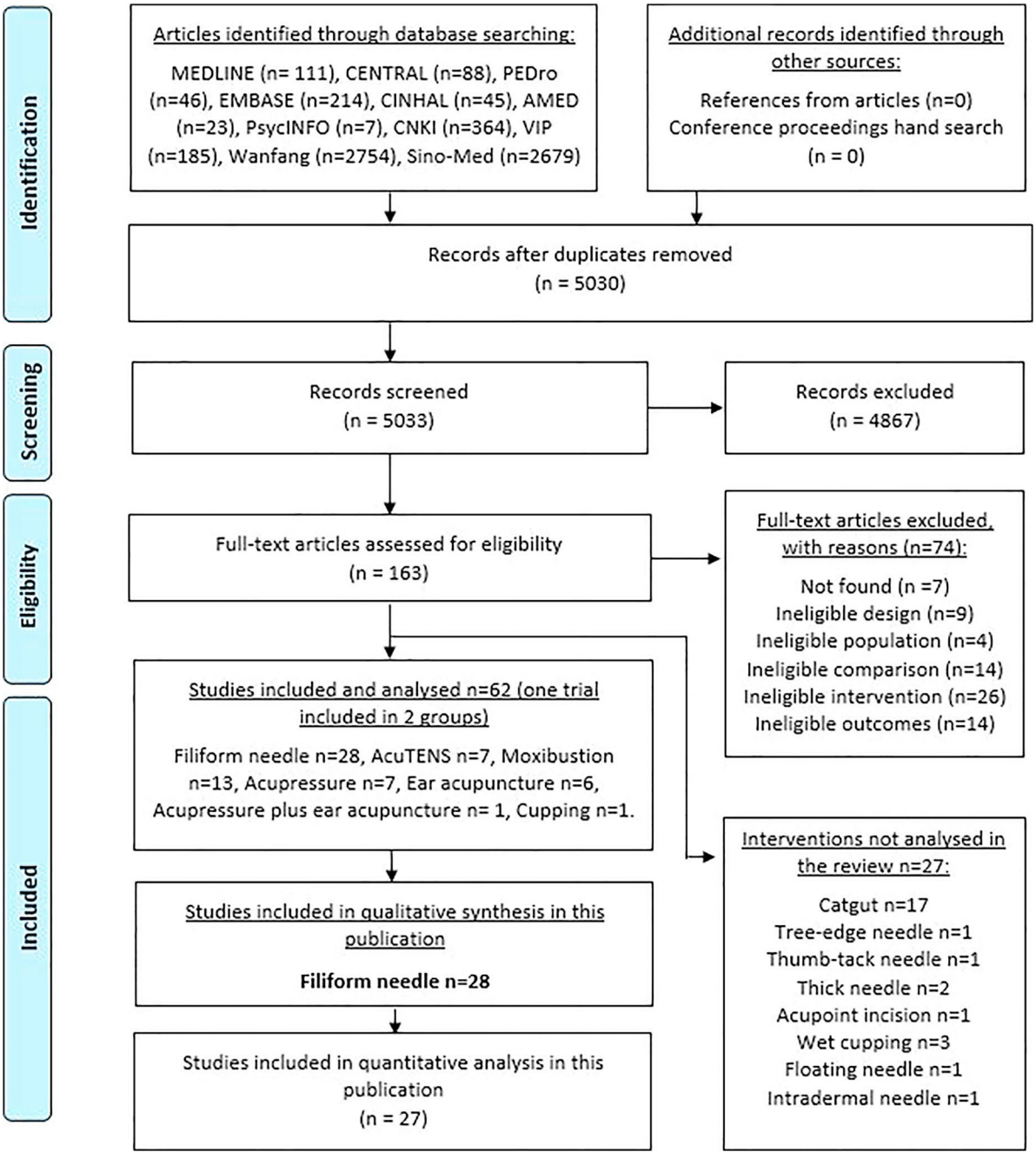

Fig. 1. Flowdiagram.

3. Results

3.1. *Study selection*

To identify potentially eligible studies, reviewers in pairs independently screened all 5030 unduplicated titles and abstracts retrieved, and full text of 166 articles were obtained for final inclusion decisions. Fifty-one articles were excluded for reasons shown in Fig. 1. As mentioned in the methods section, several acupuncture

techniques used only in China—catgut implant (17 studies), three-edge nedlee (1 study), thumb-tack needle (1 study), thick needle (2 studies), acupoint incision (1 study), wet cupping (3 studies), floating needle (1 study), or in- tradermal needle (1 study) were not included in the analysis. Eighty- eight studies were included and analysed in the review; of those, 28 used filiform needles alone or in combination with another technique, 7 used only Acupoint transcutaneous electrical nerve stimulation (AcuTENS), 13 only moxibustion, 7 used acupressure, 6 only ear acupuncture, 1 combined acupressure with ear acupuncture and 1 used a cupping technique (one trial was included in 2 groups) (Fig. 1).

As previously explained, we only focused on filiform needle technique in this paper.

3.2. *Study characteristics of filiform needle trials*

Details from the 28 trials included in the filiform needle acupuncture group are summarised in Table 1.

Twenty-seven trials were classified as parallel randomised control trials since they all described that groups were generated randomly, however, 10 trials did not describe sufficient information about the sequence generation process.[5,12,21,27,28,30–32,34,35] 1 trial was classified as a parallel quasi-randomised control trial since sequence was generated by date of admission.[22]

Table 1
Details from filiform needle studies

First author, year	Design	Subjects analysed (M/F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
	Filiform needle vs. no acupuncture Stable condition							
Deering, 2011[6]	RCT	60 (31:29) Stable within the last 4-6 weeks	I: 65.1 (9.7) C: 67.7 (5.3)	LI11, LI10, SJ10, SJ6, LU5, LU7 + Pulmonary rehabilitation	Pulmonary rehabilitation + a recommendation of 3 additional days of unsupervised home exercise (30 min)	20 min	Once a week for 7 weeks	Dyspnoea (Borg, mMRC) QoL (SGRQ) Exercise capacity (ISWT) lung Function (FEV_1%, FVC-%, IVC-%, PiMax) Postintervention and 3 months follow up
Deng Y 2019[26]	RCT	86 (49:37)	64.28 (3.61) 64.96 (3.27)	BL12, Dingchuan (EX-B1), RN17, BL13, ST40, SP10, LU5 Warm needle acupuncture +Regular medication and aerobic treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	3 to 5 times per week for 4 weeks	Exercise capacity (6mwd) Lung function (FEV_1-L, FEV_1/FVC, PEF) Postintervention
Xu J, 2004[25]	RCT	44 Moderate and severe	I: 61.0 (20.2) C: 60.0 (34.8)	Major acupoints: BL13, BL43, BL23, ST36, KI3, LU9 + 1-2 matching acupoints: Dingchuan (EX-B1), CV17, LU5, LU7 Twisting, lifting and thrusting after the arrival of qi + Bronchodilators, anti-inflammatory and anticholinergic drugs + Pulmonary rehabilitation	Bronchodilators, anti-inflammatory and anticholinergic drugs +Pulmonary rehabilitation (Walking at 60 m/min 10 to 30 min and up to 80/min for 23-30 min, and diaphragmatic breathing)	I: 30 min C: 1 h	A: 50 sessions every 2 days for 100 days	lung Function (FEV_1-%, FEV_1/FVC, TLC-%, RV-%, RV/TLC) Postintervention
Li L 2017[33]	RCT	90 (51:39)	I: 62.74 (2.15) C: 65.81 (2.75)	BL23, CV17, Dingchuan (EX-B1), BL43, ST36, LU5, ST40, SP10 Warm needle acupuncture +Regular medication and aerobic training	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	3 to 5 treatments per week for 4 weeks	Lung function (FEV_1-% and L, FEV_1/FVC) Postintervention
Liu XL, 2015[17]	RCT	59 (36:23) Mild and moderate	56.51 (6.96)	GV14, BL13, BL17, BL20, BL23 Warm needle acupuncture +Routine treatment	Routine treatment: tiotropium inhalation	30 min	Once every 2 days for one month (15 sessions)	QoL (CAT) lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Wang LL, 2013[28]	RCT	80 (68:12) Not mentioned	I: 67.21 (7.7) C: 66.5 (8.8	BL13, BL20, BL23, CV17, BL26, BL43, EX-B1, LU9, KI3, ST36, PC6, CV22, CV12, SP9, GV20, EX-HN1, HT7. + Pulmonary rehabilitation	Pulmonary rehabilitation (bronchodilators and breathing exercises)	Not mentioned	Once a day for 2 months	Dyspnoea (SGRQ, mMRC, Borg) Exercise capacity (6MWD) Lung function (FEV_1-%) Postintervention
Xie JH, 2014[15]	RCT	80 (40:40) Not mentioned	I: 68.9 (8.7) C: 68.5 (9.6)	Major acupoints: ST36, BL13, Dingchuan (EX-B1). + Matching acupoints: BL43, BL15, GV14, BL12 Warm needle acupuncture at back acupoints and ST36 + Bronchodilators and anti-inflammatory drugs	Bronchodilators and anti-inflammatory drugs	30 min	I: 24 sessions 3 times a week for 8 weeks Drugs: 2 a day for 8 weeks	lung Function (FEV_1-%, FEV_1/FVC, PEF) Postintervention
Yang JG, 2016[16]	RCT	61 (37:24) Not mentioned	57.97 (8.09)	Warm needle acupuncture at GV14, BL13, BL17, BL20, BL23. + Drug treatment	Drug treatment	30 min	14 sessions, once every 2 days	QoL (CAT) Lung function (FEV_1-%, FEV_1/FVC) Postintervention
Yang P, 2009[14]	RCT	80 (54:26) Not mentioned		Major points: ST36, SP6, CV4, Dingchuan (EX-B1. For excessive accumulation of phlegm dampness type: ST40, BL13 For extinverted blood type: SP10	+ Body exercise and healthy education	30 min	40 sessions, once daily for 20 days, 10-day interval	QoL (QOLS) Exercise capacity (6MWD) lung function (FEV_1-%, FEV_1/FVC) Postintervention

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Table 1 (*continued*)

First author, year	Design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
				For deficiency of kidney-yang: KI1 For deficiency of yin: LR3 Moxibustion therapy for bilateral ST36 + Body exercise, healthy education				
Zhan WX 2013[23]	QRCT	60 Moderate to very severe	I: 67.13 (7.88) C: 66.03 (8.45)	CV17 and CV19 + Usual treatment	Usual treatment (anti-inflammatory, eliminating phlegm drugs, symptomatic treatment)	3h	Once a day for 10 days	QoL (SGRQ) Exercise capacity (6MWD), Lung function (FEV_1-%) Postintervention
Zhu J 2017[24]	RCT	68 (42:26)	62.94 (7.56) 63.18 (6.73)	ST36, BL23, BL43, BL12, CV17, Dingchuan (EX-B1 Warm needle acupuncture + Regular treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	Once a day 5 times per week for 3 months	Lung function (FEV1-L, FVC-L, FEV1/FVC) Postintervention
Exacerbated condition								
Chen ZY 2013[25]	RCT	47 (51:5) * Not mentioned	72.43 (6.53)	General points: GV20, EX-HN1, ST9, LI18, SJ17, GB21, Zhibe, Wei, Qi (Ex-CA), LU9, PC6, ST36, GB34, ST37, SP9, Shen (EX-HN1) Special points: Cough asthma: Zhike Bosom frowsty and flustered: CV22, ST18 ST16. Tonifying five Zang organs: LR13. Tonifying six hollow organs: CV12. Tonifying Qi: CV17, CV6. Enriching the blood: SP10, BL17. + Usual treatment	Usual treatment	40 min	7 sessions for 14 days (once every 2 days)	QoL (CAT) Lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Dai L 2018[32]	RCT	68 (65:3)	66.46 (5.41) 66.79 (5.59)	Bilateral BL13, BL15, BL18, BL20, BL22, SP6, ST40, HE7 and DU20, +Symptomatic treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	30min	Once a day for 14 days (14 sessions)	Lung function (FEV_1-%, FVC-%, FEV1/FVC) Postintervention
Gao YM 2014[33]	RCT	62 (35:27) Moderate and sever	I: 67.5 C: 68.2	Dingchuan (EX-B1) with electroacupuncture stimulation (20 times/min, maximum tolerance) + Basic treatment	Basic treatment (anti-infection treatment, continuous low flow oxygen therapy, reducing phlegm and spasmolytic drugs)	20-25 min	20 sessions, once a day first 10 days. Once every 2 days last 10 days	Dyspnoea (mMRC) QoL (CAT) Exercise capacity (6MWD) Lung function (FEV_1-L) Postintervention
Liu L, 2015[27]	RCT	80 (50:30) Not mentioned	60.75 (1.55)	BL13, BL20, CV6, CV4, CV17, ST36, Dingchuan (EX-B1) +Basic treatment	Basic treatment (Bronchodilator and anti-inflammatory drugs)	10 min	24 sessions, twice a week for 3 months	Exercise Capacity (6MWD) Lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Wang JY, 2015[12]	RCT	63 (35:28) Not mentioned	64.00 (4.80)	ST36, ST40, SP6, SP15, CV12, CV13, CV6, CV4, LU9, LU5, LU6, Dingchuan (EX-B1) + Ginger moxibustion with cones at CV17 and ST36 + Basic treatment	Basic treatment: bronchodilators and anti-inflammatory drugs, vitamin and oxygen uptake as adjuvant therapy and mechanical ventilation applied in very sever patients	30 min	Once a day for 40 days	Lung function (FEV_1-%, FVC-%, MVV, MIP) Postintervention
Zhang YM, 2013[23]	RCT	63 Not mentioned	I 1: 68.53 (7.58) I 2: 72.21 (7.53) I 3: 71.47 (7.48) C: 69.76 (7.21)	I1: bilateral BL13 I2: bilateral TE6 I3: bilateral BL13 and TE6 Reinforcing-reducing method + Regular treatment	Regular treatment (Oxygen 2-3 L/min; antibiotherapy, bronchodilators and mucolytic drugs)	30 min	Twice daily for 14 days	Lung Function (FEV_1/FVC) Postintervention
	Filiform needle vs. sham acupuncture							
	Stable condition							

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Table 1 (*continued*)

First author, year	Design	Subjects analysed (M/F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
Cao L, 2012[21]	RCT	29 Not mentioned	I 1: 76.6 (6.50) I 2: 72.9 (8.33) C: 77.6 (5.70)	I 1 : CV17, LU5, LU7, ST36, SP9, ST40, SP6, KI3 + Ear A (Shen Men, Fei, Qi Guan, Yan Hou, Dui Er Pin Xian) I2: CV17, LU5, LU7, ST36, SP9, ST40, SP6, KI3 +Sham Ear A + Regular treatment	Sham superficial acupuncture in same points slightly offset + Sham auricular points + Basic treatment (bronchodilator, anti-inflammatory, anti-cholinergics)	30 min	Acup: once a day, 20 sessions Ear Acup.: 3-5 times a day, 20 days	Dyspnoea (mMRC) QoL (CAT) lung function (FEV_1-%, FEV_1/FVC) Postintervention
Feng J, 2016[20]	RCT	72 (64:8) Moderate to very severe	I: 67.8 (5.4) C: 67.1 (6.1)	Bilateral: LU1, LU9, LI18, ST36, GB12, BL13, BL20, and BL23 with manual stimulation and De qi response + Regular drug treatment	Sham acupuncture using Park sham device at same real acupuncture points. + Regular drug treatment	30 min	24 sessions, 3 times a week for 8 weeks	Dyspnoea (Borg) QoL (SGRQ) Exercise capacity (6mwd), lung function (FEV_1-%, FVC-L) Postintervention
Ge Y 2017[30]	RCT	44 (38:6)	65 (6) 65 (7)	Acupuncture CV17, ST18, CV4, CV12, ST25 + electroacupuncture Regular medication and aerobic training	Sham acupuncture + sham electroacupuncture Regular medication and aerobic training	Not mentioned	14 treatments, 2 to 3 times per week	Exercise capacity (6mwd), lung function (FEV_1-%, FVC-%, FEV_1/FVC) Postintervention
Guo YM, 2013[19]	RCT	33 (30:3) Not mentioned	I: 65.28 (5.73) C: 66.60 (6.06)	CV17, BL26, CV12, bilateral ST18, ST25, ST36. Manual + electrical stimulation + Aerobic exercise	Sham acupuncture with placebo needle same points + Aerobic exercise	I: 30 min	I: 14 sessions every 2 days	QoL (QOLS) Lung function (FEV_1-%, FEV_1/FVC, FVC-%, MVV) Postintervention
Jobst, 1986[5]	RCT	24 Not mentioned	I: 67.4 (11.3) C: 61.5 (17.6)	Points according to the principles of traditional Chinese medicine + Moxibustion if indicated	Needles inserted into non-acupuncture points	Not mentioned	13 sessions over 3 weeks	Dyspnoea (Borg, SOB) Exercise capacity (6MWD) Postintervention
Ruhlemann H, 1997[31]	RCT	10 (7:3) Not mentioned	64.3 (10.4)	LU1, LU9, BL13, KI3, BI23, ST36, ST40, SP6, CV17, CV6 With De Qi sensation + Corticosteroids, long and sort beta 2 adrenergic	Superficial acupuncture needling with no de Qi, 3 cm from real points + Corticosteroids, long and short beta 2 adrenergic	Not mentioned	7 sessions in 14 days. Once every 2 days	Dyspnoea (CRQ) QoL (CRQ) Lung function (FEV_1-%, VR/TLC, MOIP) Postintervention
Suzuki, 2012[8]	RCT	68 (63:5) Stable over 3 months Moderate n = 19 Sever n = 24 Very severe n = 25	I: 72.7 (6.8) C: 72.5 (7.4)	LU1, LU9, LI18, CV4, CV12, ST36, KI3, GB12, BL13, BL20 and BL23 Manual rotation + Daily medication	Park sham device over same points as experimental group + Daily medication	50 min	Once a week for 12 weeks	Dyspnoea (Borg, mMRC) QoL (SGRQ) Exercise capacity (6MWD) Lung function (FEV_1-%, FVC-%, RV/TLC, DLCO, MIP, MEP) Adverse events Postintervention
Tong J, 2014[18]	RCT	30 (27:3) Not mentioned	I: 64 (6) C: 67 (6)	CV17, ST18, CV4, CV12, ST25, ST16 Unilateral LI4, ST40 Manual and electrical stimulation + Aerobic exercise	Sham acupuncture at same points + Aerobic exercise	30 min	10-15 sessions. 2 to 3 times a week for 5 weeks	QoL (SGRQ) Exercise capacity (6MWD) Lung function (FEV_1-%, FEV_1/FVC, FVC-%, MVV) Postintervention
	Exacerbated condition							
Whale CA, 2009[24]	RCT	9 (5:4) Not mentioned	68 (range 53-78)	Bilateral LI4 + two upper sternal points (2 cm apart in the midline, advanced to the periosteum) no manual or electrical stimulation and no attempt to elicit de qi	Park sham Device over the kneecaps bilaterally and ST25 bilaterally	20 min	3 sessions (baseline, 24 h and 48 h)	Dyspnoea (VAS, Borg scale) Anxiety (VAS) Adverse events Postintervention
	Filiform needle vs drugs Stable condition							
Gao J, 2011[13]	RCT	60 (25:35) Not mentioned	I: 64.87 (8.73)	Major acupoints: Dingchuan, BL13, ST36. + 2-3 matching acupoints: CV 17, CV22,	Bronchodilators and anti-inflammatory drugs	30 min	I: 3 times a week for 8 weeks	QoL (SGRQ) Lung function (FEV_1-%,

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Table 1 (*continued*)

First author, year	Design	Subjects analysed (M/F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
			C: 65.25 (10.66)	BL20, BL23, BL12, DU14, BL43, BL15. Warm a acupuncture, two sticks for every point			C: twice daily for 8 weeks	FEV_1/FVC, PEF) Postintervention
Yang J 2018[33]	RCT	61 ()		Dinghuan (EX-B1), BL13, ST36	Inhaled Seretide	Not mentioned	3 times a week for 8 weeks	QoL (SGRQ) Lung function (FEV_1-% and L, FEV_1/FVC, PEF) Postintervention

RCT: randomised control trial; QRCT: quasi-randomised control trial mMRC modified medical research council; SGRQ: St George's respiratory questionnaire; ISWT: Incremental Shuttle Walking Test; QoL: quality of life; CAT: COPD assessment test; FEV_1: : forced expiratory volume in one second; FVC forced vital capacity; QOLS: quality of life scale; MVV: maximal voluntary ventilation; TLC total lung capacity; RV: residual volume; SOB shortness of breath; 6MWD: 6-minute walking distance; CRQ: chronic respiratory questionnaire; MOOP: mouth occlusive Inspiratory pressure; MEP: mouth expiratory pressure; IVC: inspiratory vital capacity; PIMAX: maximal inspiratory muscle pressure.

Age of participants ranged from 56 to 77 years. Patient's severity wa poorly reported, but it ranged from mild to very severe in the trials that did report it. After reading each paper carefully, 21 trials were classified as treating stable patients,[5,6,8,13–19,21,23,25,28–31,33–36] and 7 trials were classified as treating exacerbated patients.[12,20,23,24,26,27,32]

We found great heterogeneity in the filiform acupuncture protocols used in every trial. These differences included combining filiform needle with other techniques, the number of acupuncture points used, the length of the stimulation time and the duration of the study.

Filiform needle technique was used in combination with other techniques in 15 trials: combined with moxibustion in 10 trials,[5,11–16,34–36] with electroacupuncture in 4 trials[18–20,30] and with ear acupuncture in 1 trial.[21] Study duration ranged from 3 to 12 weeks with a treatment regime from once a day to once a week. Stimulation time was 20 to 40 min for most studies, and only 2 studies reported longer stimulation periods:

Suzuki (50 min)[6] and Zhan (3 h).[22] Most of the trials used 6 to 12 points in their treatments, and only 3 studies[22–24] used fewer than 4 points. Acupuncture points were described as a fixed protocol in most trials, and only 5 used flexible protocols.[13–15,25,26] Most frequently used acupuncture points were ST36 (15 trials), BL13 (14 trials) and Dingchuan (EX-B1) and BL23 (12 trials).

In 17 trials, filiform needle acupuncture was added to usual treatment and compared with usual treatment alone.[8,12,14–17,20,22,23,25–28,32–36] Sham intervention was used in 9 trials using diverse procedures: non-penetrating needles at real points,[6,18,19,29,30] slightly offset points,[21] irrelevant points,[24] superficial needling at real points [31] or needling at non-acupuncture points.[5] Finally, regular drugs were chosen as a comparator in 2 papers.[13,33]

All trials assessed all outcomes at the end of the intervention and only one had 3 months follow up.[8]

3.3. *Risk of bias within studies*

Assessment of risk of bias of the included filiform needle trials is summarised in Fig. 2. Due the nature of filiform needle intervention, the Cochrane risk of bias tool was modified to add "blinding of outcome assessment". "Blinding of personnel" was removed due the fact that the person performing the acupuncture treatment cannot be blinded. In general, most of the studies had an unclear risk of bias due to the lack of information reported. Allocation concealment was one of the most critical aspects with only 4 trials (14.2%) classified with a low risk of bias. Blinding of outcome assessment was poorly described in most trials, only 6 (21.4%) were classified with a low risk of bias. Detailed risk of bias information of each trial is reported in additional file 2

3.4. *Synthesis of results of filiform needle acupuncture*

Of the 28 trials included in the synthesis of the results, only 27were in the quantitative analysis, one trial was excluded for all meta-analysis due to important inconsistencies in the reported results.[29] To assess filiform needle acupuncture efficacy, 3 different comparison groups were formed: filiform needle vs. no acupuncture, filiform needle vs. sham and filiform needle vs. drugs. In each meta-analysis, patients in stable and exacerbated conditions were separated in subgroups to identify if those patient's characteristics could generate heterogeneity in our results. When possible, results combining the two subgroups are given; otherwise, results for the subgroups are presented

3.4.1. Filiform needle vs. no acupuncture

Seventeen trials compared the efficacy of filiform needle with a group not receiving any acupuncture intervention.[8,12,14–17,20,22,23,25–27,32,34–36]

3.4.1.1. Dyspnoea. Three trials assessed dyspnoea in this comparison—2 including stable patients[8,26] and 1 including exacerbated patients.[20] The Borg scale was used in 2 trials, while the modified Medical Research Council (mMRC) scale was used in all 3 trials. According to the American thoracic society/European respiratory society (ATS/ERS) Task Force, we analysed separately short term (Borg, Visual analogue scale (VAS), Short of breath (SOB)) and situational (mMRC) dyspnoea.[31]

Meta-analysis did not show statistical differences on the Borg scale (2 trials, 121 stable participants) (MD: -0.38; 95% CI: -0.8, 0.04; I^2 = 0%) (Fig. 3.a) nor for the mMRC scale pooling stable and exacerbates subgroups (3 trials, 183 patients) (MD: 0.12; 95% CI: -0.20, 0.43; I^2 = 58%) or analysing the two subgroups separately (Stable condition, 2 trials, MD: 0.07; 95% CI: -0.48, 0.62; I^2 = 67%) (Exacerbated condition, 1 trials, MD: 0.22; 95% CI: -0.02, 0.46) (Fig. 3.b).

3.4.1.1. Quality of life. Eight trials studied filiform needle effect plus regular treatment on quality of life compared with regular treatment alone. Six trials included stable patients,[8,14,16,17,22,27] while 2 trials included exacerbated patients.[20,26] Of the 8 trials, 3 used the St. George's Respiratory Questionnaire (SGRQ),[8,17,22] 4 trials used the COPD Assessment Test (CAT)[16,20,26,27] and 1 trial used the Quality of Life Scale (QoLS).[14]

For this comparison, a standardised mean difference was used, but we found great heterogeneity (I^2 = 94%). When exploring it, it was found to be due to one single trial (which results seemed to over- estimate acupuncture's benefits compared with other trials). [14] After removing this trial, results showed a significant improvement on QoL (7 trials, 421 patients) (Std. MD: -0.62; 95% CI: -0.90, -0.34; I^2 = 50%),
this result was seen for the stable subgroup (5 trials) (Std. MD: -0.64; 95% CI: -1.03, -0.26; I^2 = 62%) and the exacerbated subgroup (2 trials)
(Std. MD: -0.54; 95% CI: -0.94, -0.15; I^2 = 15%) (Fig. 3.c).

3.4.1.1. Exercise capacity. Seven trials assessed exercise capacity, with 5 trials including stable patients [8,14,22,28,36] and 2 trials including exacerbated patients.[20,27] Exercise capacity was measured with the 6-minute walking test (6MWT) in 5 trials,[14,20,22,27,28] while the incremental shuttle walking test (ISWT) was used in only 1 trial,[8] for the meta-analysis this last paper was not included because tests measure different physiological responses.
Meta-analysis of trials using 6MWT showed high heterogeneity (I^2 = 88.6%). For stable patients subgroup (4 trials, 306 participants) heterogeneity was still too high (I^2 = 73%), but was reduced when removing trial from Zhan W,[23] which seamed to be outperforming, and results remained statistically significant (6MWT MD: 33.05 m; 95%CI: 19.11,46.99; I^2 = 67%).No statistical difference was seen in ex- acerbated patients (2 trials, 142 participants) (6MWT MD: 0.65 m; 95% CI: -20.74, 22.04; I^2 = 20%) (Fig. 3.d).

3.4.1.2. Lung function. Lung function was assessed in 15 trials using the forced expiratory volume in one second (FEV_1) and/or FEV_1 and forced vital capacity ratio (FEV_1/FVC). All 15 trials assessed FEV1: 11 trials including stable patients[8,14–16,22,25,27,28,34–36] and 4 including exacerbated patients.[12,26,27,32] Eleven trials also assessed FEV_1/FVC: 7 trials including stable patients[14–16,25,27,34,36] and 4 including exacerbated patients.[23,26,27,32]

The study by Jia et al[25] was not pooled in the FEV_1 and FEV_1/FVC meta-analysis due to the fact that the SD reported was drastically smaller than in the other trials. Contact with the author to solve this issue was not possible.

For FEV_1, 12 trials reported FEV_1 in % while 2 of them only reported litres (L).[34,36] Pooled results from trials reporting FEV_1 in % showed great heterogeneity due to the trial from Li et al,[35] outperforming the rest of the trials. When removing this trial meta-analysis did show a small but statistical significant improvement of 1.58 perceptual points on FEV_1% (11 trials, 729 participants) (95% CI: 0.51, 2.66; I^2 = 0%), this improvement was seen in the exacerbated subgroup (4 trials, 237 participants) (MD: 3.09; 95%CI: 1.00, 5.18, I^2 = 0%) but not in the stable subgroup (7 trials, 472 participants) (MD: 1.04; 95%CI: -0.21, 2.29, I^2 = 0%) (Fig. 3.e).

For FEV_1/FVC, the 10 trials were not meta-analysed due to high heterogeneity between the stable and exacerbated subgroups (I^2 = 77%). For the stable patients subgroup,[14–17,25,34,36] results showed no statistical difference between groups but heterogeneity was too high (I^2 = 83%), removing trial from Deng et al[36] reduced hetero- geneity but results remained non-significant (5 trials, 349 participants) (FEV1/FVC MD: 1.33; 95% CI: -1.19, 3.85; I^2 = 38%). In the ex-acerbated subgroup, differences were found based in 4 trials[23,26,27,32] (330 participants) (MD: 3.42; 95% CI: 1.55, 5.29) (Fig. 3.f).

3.4.2. Anxiety and depression

No trial assessed anxiety or depression.

3.4.3. Filiform needle vs. Sham

Nine trials compared filiform needle with a sham intervention, with 8 trials including stable patients[5,6,18,19,21,29–31] and only 1 including exacerbated patients.[24]

3.4.3.1. Dyspnoea. Six trials studied the effect of filiform needle compared with sham acupuncture, with 5 trials including stable patients[5,6,21,29,30] and only 1 including exacerbated patients.[24] The Borg

scale was used in 4 trials,[5,6,24,29] mMRC in 2 trials,[6,21] and SOB,[5] chronic respiratory questionnaire (CRQ)[31] and VAS[24] in one trial each.

Three trials measured short-term dyspnoea, two including stable parti- cipants[6,30] and one with exacerbated participants.[24] Heterogeneity was too great to plot all 3 studies ($I^2 = 77\%$). For stable participants standardised

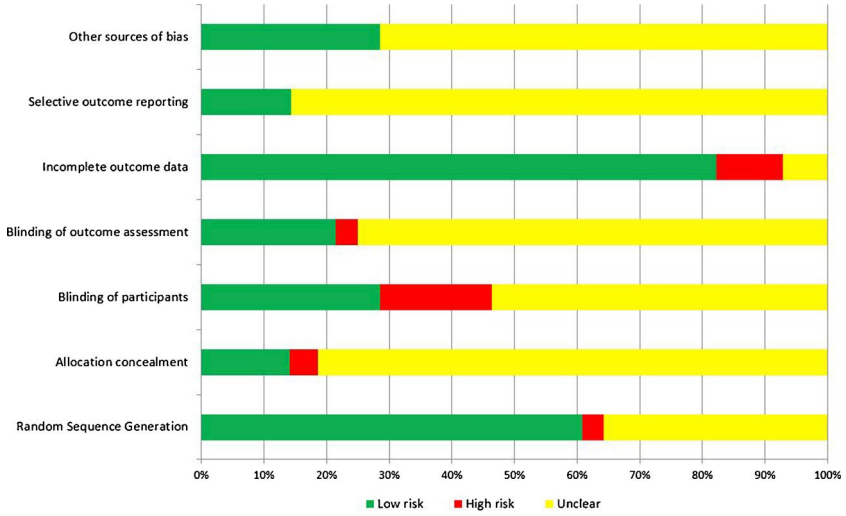

Fig. 2. Risk of bias of included studies.

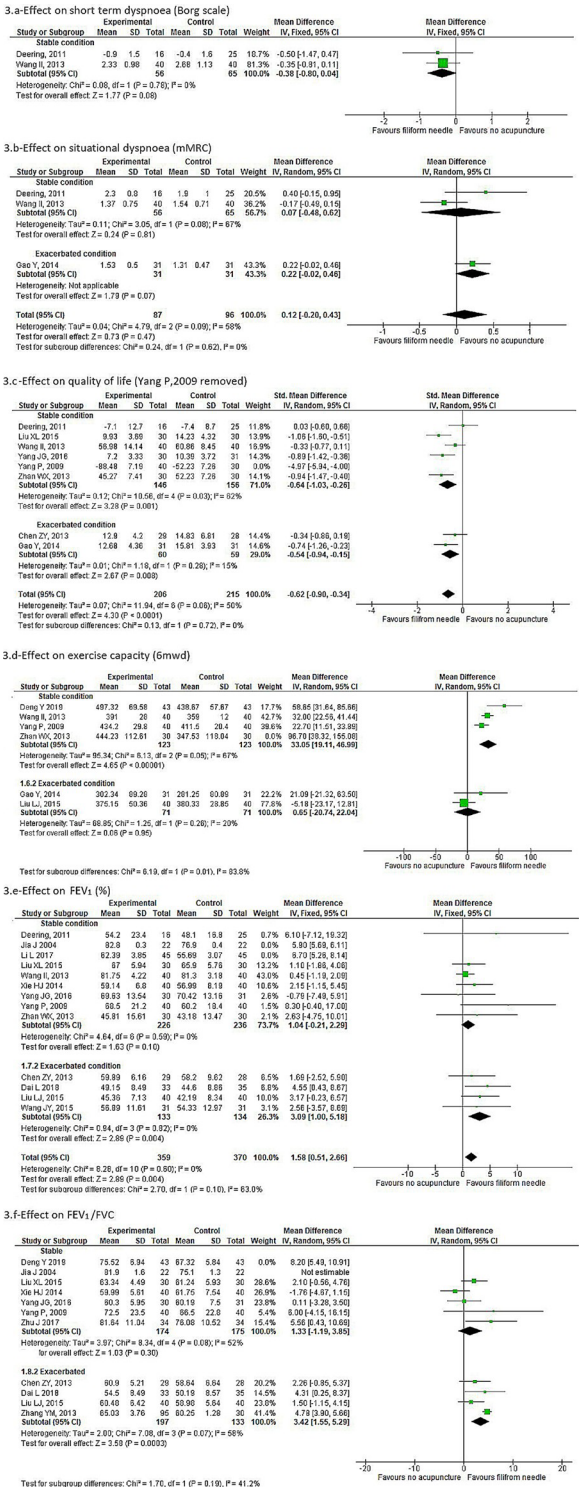

Fig. 3. Meta-analysis of filiform needle vs. no acupuncture.

mean difference showed a statistical benefit of real acupuncture using Borg and SOB measures (Std MD: -1.07; 95% CI: -1.58, -0.56; I^2 = 11%; 70 participants) (Fig. 4.a). For exacerbated participants no statistical differences where observed in a small pilot trial of only 7 patients.

Two trials reported situational dyspnoea both in stable patients (6,21,). Results showed a statistical reduction of 0.77 points on the mMRC scale (95% CI: -1.14, -0.41; I^2 = 26%) (Fig. 4.b).

Two trials were not included in the meta-analysis—Feng[29] as previously explained and Jobst, [5] since data was presented as median and range instead of mean and standard deviation.

3.4.3.2. Quality of life. Quality of life was assessed in 6 trials, all including stable participants.[6,18,19,21,29,31] The SGRQ was used in 3 trials,[6,18,29] and the CAT,[21] QoLS[19] and CRQ[31] were used in one trial each. Meta-analysis of 5 trials (176 participants)[6,18,19,21,30] shows an overall improvement in the real filiform acupuncture group (Std. MD: -0.81; 95% CI:-1.12, -0.49; I^2 = 24%) compared with sham intervention (Fig. 4.c).

3.4.3.3. Exercise capacity. Five trials assessed exercise capacity, all with stable patients and using the 6MWT.[5,6,18,29,30] Four trials that underwent meta-analysis showed a clinically significant increase of 76.68 m in the 6MWT in the real filiform acupuncture group compared with sham acupuncture (158 participants; 95% CI: 39.93, 113.43; I^2 = 0%) (Fig. 4.d). Feng's trial was not included.[29]

3.4.3.4. Lung function. Seven trials assessed lung function, all including stable participants.[6,18,19,21,29–31] Of those, all 7 trials reported FEV [6,18,19,21,29–31] and 5 reported FEV /FVC.[18,19,21,29,30] Pooled results for FEV_1 showed an improvement of 5.40 percentage points in the real acupuncture group compared with sham acupuncture (6 trials, 267 participants) (95% CI: 2.90, 7.91; I^2 = 0%) (Fig. 3.e). This improvement was also observed in FEV_1/FVC [18,19,21,31] (4 trials, 140 participants) (MD: 6.64; 95% CI: 3.44, 9.83; I^2 = 10%) (Fig. 4f[29].

3.4.3.5. Anxiety and depression. Only one small pilot trial with only 9 participants assessed depression using the VAS,[24] sample was too low to draw any conclusion. Depression was not assessed in any trial.

3.4.4. Filiform needle vs. conventional drugs

Only 2 papers compared filiform needle technique with conventional drugs (Seretide), both of them with stable participants.[13,33]

3.4.4.1. Exercise capacity. Two trials, both with stable participants analysed QoL using the SGRQ. Meta-analysis showed a statistical reduction of 4.77 points (120 participants) (95% CI: -8.50, -1.03; I^2 = 60%) (Fig. 5a)

3.4.4.2. Lung function. Two trials with stable participants assessed lung function, both using FEV_1% and FEV_1/FVC (13.33). Pooled results from FEV_1 and FV_1/FVC showed no significant difference compared with Seretide inhalation (120 participants) (FEV_1% MD: 0.00; 95% CI: -2.36, 2.35; I^2 = 0%) (Fig. 5b) (FEV_1/FVC MD: -1.70; 95% CI: -3.90, 0.50; I^2 = 0%) (Fig. 5c)

3.5. Adverse events

Adverse events of filiform needle technique were only assessed in 2 trials. For stable patients, Suzuki et al[6] reported 5 cases of subcutaneous haemorrhage and 5 cases of pain in the puncture site out of 30 participants in the real filiform needle acupuncture group. Other minor reactions like fatigue or dizziness were equally reported in the real and sham acupuncture group. For exacerbated patients, Whale et al[24] reported no side effects in the 4 participants receiving real filiform needle acupuncture. Not enough data was reported to calculate risks for each event.

3.6. Publication bias

Only one meta-analysis included more than 10 trials (Filiform needle vs no acupuncture for FEV_1). Funnel plot did not show evidence of publication bias (Additional file 3).

4. Discussion

4.1. Main results

From our knowledge, this is the first systematic review that evaluates specifically the effectiveness of filiform needle acupuncture for

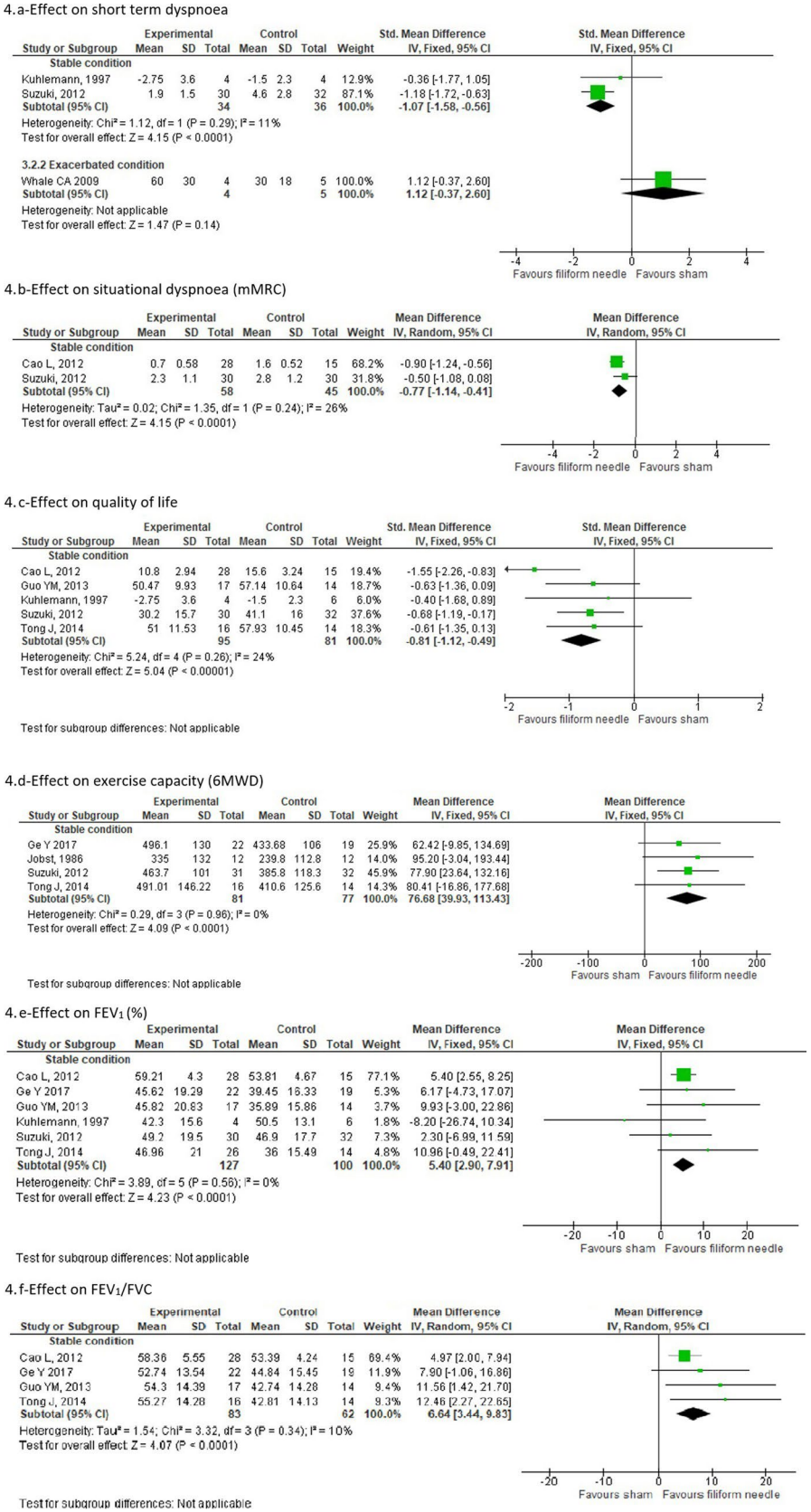

Fig. 4. Meta-analysis of filiform needle vs. sham.

COPD. Benefits were observed for stable patients with regard to dyspnoea, QoL and exercise capacity compared with sham. Those benefits were also seen in QoL and exercise capacity when the comparator was no acupuncture. For lung function, mixed results were obtained, but results that were statistically significant were not clinically relevant. Anxiety was only assessed in one small pilot trial and no conclusions could be drawn while depression was not studied in any trail.

Twenty-eight trials assessing the efficacy of filiform needle acupuncture were included in this systematic review. Participants were adults and older adults with stable and exacerbated conditions. Comparison groups were no acupuncture, sham acupuncture and drug treatments. Treatment protocols were very heterogeneous and included different types and numbers of acupuncture points, different treatment regimens and different durations.

4.2. *Implications for clinical practice*

First, there is remarkable clinical diversity coming from acupuncture interventions. However, this reflects the common heterogeneity that exists in acupuncture's clinical practice and the lack of consensus about the best treatment for COPD, especially regarding duration and regime. From this observation, it should be strongly considered to create con- sensus about interventions and measures for future studies.

Second, dyspnoea results show that filiform needle acupuncture could have a beneficial effect especially in stable COPD patients when compared with sham acupuncture. This effect could be produced through the enhancement of the endogenous opioid system produced by acupuncture,[37] as endogenous opioids modulate dyspnoea in patients with COPD.[38] However, we observed better results in trials that evaluated dyspnoea at short term (Borg, VAS and SOB) than others evaluating situational dyspnoea (mMRC). We believe this could be due the fact that the mMRC is relatively insensitive to change due to therapeutic inteventions such as acupuncture.[39,40] This difference between scales is also observed when acupuncture is compared with no acupuncture, where better results were also observed on the Borg scale compared to mMRC even though none of them was statistically significant.

ConceCVing QoL, both comparisons show a positive effect of acupuncture in COPD patients, independent of the instrument used (SGRQ, CAT, or QoLS). According to dyspnoea effects, a better perception of breathlessness perceived by patients could be a strong explanation of the improved QoL.[41] This effect is also perceived for the exacerbated patients and could confirm the role of dyspnoea in relation to QoL.

For exercise capacity, most of the studies used the 6MWT. This is a submaximal test that reflects the capacity to maintain daily physical activity.[42] Surprisingly, in stable patients the observed increase in walking distance is very high, 76 m (vs. sham comparison) and 33 m (vs. no acupuncture comparison), surpassing the minimum clinically important difference (30 m)[43] in both cases. Suzuki and co-workers demonstrated in different studies that acupuncture could reduce respiratory accessory muscle tension and increase oxygen saturation,[6,44] both circumstances could produce an important relief of the respiratory symptoms during walking favouring the improvements in distance.

Finally, the analysis of filiform needle acupuncture in pulmonary function (FEV_1 and FVC), even though statistically significant in some comparisons, does not show clinically relevant benefits. Those effects could be related to an activation of the autonomic nervous system when acupuncture is applied (decreasing bronchospasm) (6) but wouldn't be enough to be perceived as an improvement by patients.

It is of note that more outcomes had positive results when compared with a sham intervention than compared with no intervention. Even outcomes that were positive in both comparisons, like QoL and FEV_1, were greater in the sham comparison than in the no intervention comparison. Usually trials not using sham procedures tend to over- estimate the real effect of the intervention due to patients' expectations, especially for self-reporting outcomes like dyspnoea and QoL. A pos- sible explanation for this could be the small size of the trials, the het- erogeneity of the intervention, the different characteristics of the in- cluded participants and the baseline treatments received. Those differences may lead to the different efficacies obtained for

each trial. Higher quality trials (trials using sham) might have been better de- signed, and those factors had less of an impact on the results; therefore, results could be meta-analysed and CIs were smaller. Acupuncture seems safe for COPD patients, since only minor adverse events were described; however, the reporting of this outcome was really poor.

4.3. *Relation with prior works*

During the review process, two other similar works on this topic had been published by Coyle et al[9] and Wang et al[45]

In the first review 16 trials were included and concluded (that compared with placebo) acupuncture therapies could result in clinically significant improvements in dyspnoea, QoL and distance walked, but no benefit was observed in measures of lung function. When comparing our analysis with this review, similar results are observed confirming the acupuncture benefits in COPD. However, there are several differences between both reviews. Firstly, because Coyle et al included all kinds of acupoint stimulation interventions (even pharmacological ones) and only 5 of the 16 included trials used filiform needle acupuncture, all 5 trials have been included in our review.[5,6,13,24,31] Secondly, even pooling all the interventions together, Coyle's meta-ana- lysis included a maximum of 5 trials, which decreased the statistical power and introduced an important confusion factor on the results. In the present review, we focused exclusively on filiform needle technique and the number of included trials of this technique was huge (28 vs. 5). These differences could be attributed to the fact that 19 of the included trials were published after 2013, when Coyle et al finished their data- base search. Finally, to try to avoid possible heterogeneity due to the different effect that acupuncture could have depending on a patient's state, we decided to do subgroup analyses for stable and exacerbated COPD patients.

In the second review Wang et al included 19 trials using filiform needle acupuncture techniques, such as manual acupuncture, electro- acupuncture, warm acupuncture and ear acupuncture. In this review meta-analysis showed an improvement in the exercise capacity but not on quality of life using the overall score of the SGRQ. We believe these differences could be due to several factors. First, we included trials using filiform needle alone or in combination with other techniques such as any kind of moxibustion, which is very common in clinical practice, Wang et al however, only included warm acupuncture technique. Second, Wang et al plotted together body acupuncture and ear acupuncture whereas we examined ear acupuncture techniques sepa- rately. Finally, Wang's review only included trials with participants in stable condition.

4.4. *Strengths and limitations*

This is the most complete and extended systematic review on this topic to date. We included 7 international and 4 Chinese databases and no language restriction was applied. We strictly followed the review protocol during the study selection process and data extraction and analysis, even though we finally decided to publish the results in two separate papers due to the great amount of information obtained. This is the first review that separately analyses different acupuncture techniques and patient's conditions (stable and exacerbated). We decided not to plot all interventions together, because they may have different action mechanisms and, therefore, different effects in different clinical conditions. Regarding this, since in clinical practice most practitioners use filiform needle technique alone or in combination of other interventions, we plotted together trials following this practice.

For the limitations, we could not find any extra papers through hand searching, probably because we only explored American and European international congresses but not Chinese. However, the CNKI database includes Chinese conference proceedings and unpublished academic theses. We also could not review 7 trials, because it was impossible to obtain full text articles. We also could only asses publication bias based on one meta-analysis due to the small number of trials included in each comparison. Finally, important heterogeneity was found in many comparisons, this could be due differences in the treatment protocols and lack of trials quality, reducing the confidence in the results, for this reason we did not perform meta-analysis

when heterogeneity was too high (over 70%).

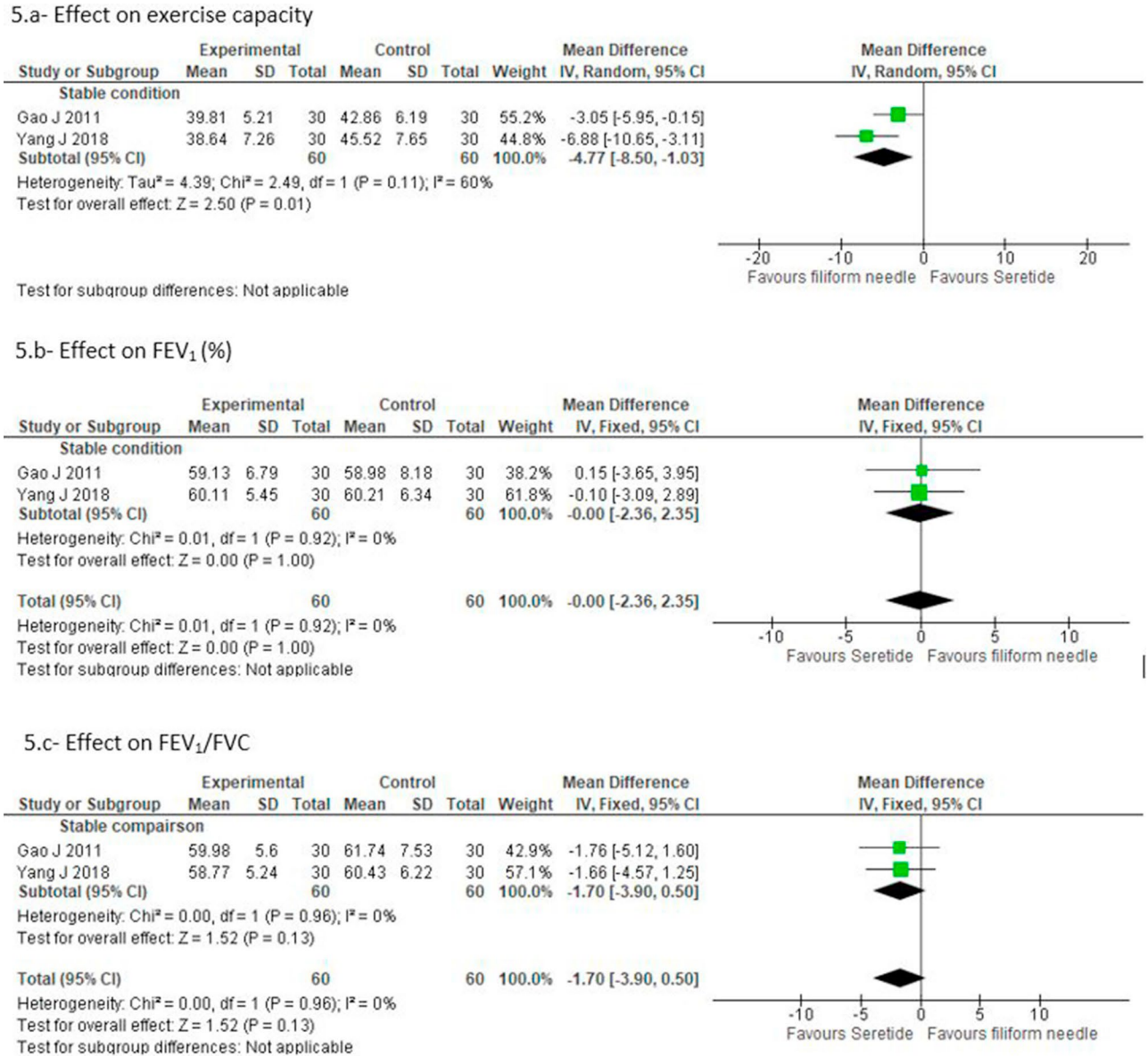

Fig. 5. Meta-analysis of filiform needle vs. drugs.

It is important to remark that even though we just included trials using filiform needle technique, in 15 trials this was used in combination with other techniques such as moxibustion or electrical stimulation (electroacupunture). We decided not to analyse those trials separately since these would have led to multiple very small groups making the analysis and interpretation of the results much more difficult.

5. Conclusions

This review found that in stable COPD patients, filiform needle acupuncture added to

usual treatment improved dyspnoea, QoL and exercise capacity compared with a sham. Those benefits were also seen in QoL and exercise capacity when the comparator was no acupuncture. For lung function, mixed results were obtained, but those statistically significant were not clinically relevant.

We found great heterogeneity in treatment protocols, which included different types and numbers of acupuncture points, different treatment regimens and different treatment durations. Due the low methodological quality of some of the included trials and the low number of trials included in some comparisons such as dyspnoea, these results should be interpreted with caution. Further large well-designed randomised control trials are necessary to corroborate the effectiveness of filiform needle acupuncture in COPD.List of AbbreviationsAcuTENSAcupoint transcuta- neous electrical nerve stimulationATS/ERSAmerican thoracic society/ European respiratory societyCATCOPD Assessment TestCIConfidence intervalCOPDChronic obstructive pulmonary diseaseCRQChronic re- spiratory questionnaireFEV_1Forced expiratory volume in the first secondFVCForced vital capacityMDMean differencemMRCModified Medical Research CouncilQoLSQuality of Life ScaleSGRQSt. George's Respiratory QuestionnaireSOBShort of breathStd. MDStandardized mean differenceTSWTIncremental shuttle walking testVASVisual analogue scale6MWT6-minute walking test

List of Abbreviations

AcuTENS Acupoint transcutaneous electrical nerve stimulation
ATS/ERS American thoracic society/European respiratory society
CAT COPD Assessment Test
CI Confidence interval
COPD Chronic obstructive pulmonary disease
CRQ Chronic respiratory questionnaire
FEV_1 Forced expiratory volume in the first second
FVC Forced vital capacity
MD Mean difference
mMRC Modified Medical Research Council
QoLS Quality of Life Scale
SGRQ St. George's Respiratory Questionnaire
SOB Short of breath
Std. MD Standardized mean difference
TSWT Incremental shuttle walking test
VAS Visual analogue scale
6MWT 6-minute walking test

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JV and MS made substantial contributions to the conception and design of the review, extraction, analysis and interpretation of the data and writing and reviewing the manuscript. YF, and CW and JL are responsible for the Chinese language electronic search, and data abstraction and contributed to the writing and reviewing of the manuscript. NH, RX, XT, RH, MY, NG and MS, are responsible for trials inclusion, data extraction and critically reviewing the final manuscript.

All authors read and approved the final manuscript.

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Carles Fernández is a PhD candidate from the Methodology of Biomedical Research and Public Health program at the Universitat Autonoma de Barcelona.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.ctim.2019.08.016.

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