SOUTH BAYLO UNIVERSITY

Effect of Acupuncture and Oriental Medicine for Lung Functions on Bronchial Asthma: A Systematic Review and Meta-Analysis

By

Kyouhwan Han

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DISSERTATION OF KYOUHWAN HAN

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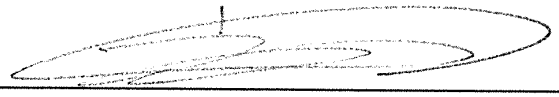

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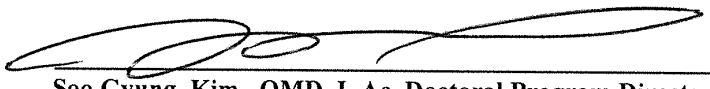

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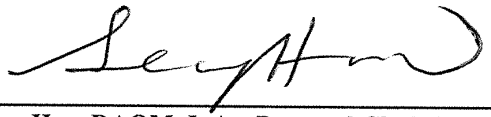

Seong Hwa Hue, DAOM, L.Ac, Doctoral Clerkship Coordinator

Joseph H. Suh, Ph.D, OMD, L.Ac, Doctoral Research Coordinator, Professor

South Baylo University

Anaheim, California

June 13, 2019

for my family

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Kyouhwan Han

SOUTH BAYLO UNIVERSITY at ANAHEIM, 2019

Research Advisor: Jeajong Kim, MD, OMD, L.Ac

ABSTRACT

Acupuncture and Oriental medicine (AOM) with a long history of more than 2,500 years is recently the major component of complementary and alternative medicine (CAM) in the world and still used for chronic asthma as a monotherapy or in integrated medicine in Asian countries. In order to evaluate the effect of AOM for lung functions such as FEV1, FVC, FEV1/FVC, and PEF on bronchial asthma, a systematic review and meta-analysis were performed with nine randomized controlled trials (RCTs) involving seven eligible studies which were searched from PubMed, Cochrane Library, EBSCO *host*, and other relevant sources from January 2019 through March 2019. And the experiment comprises three AOM modalities of herbs, acupuncture, and moxibustion. The risks of bias were assessed using the Cochrane Risk of Bias Assessment Tool for the methodological quality of the included studies. For the meta-analysis, were used RevMan 5.3 software, standardized mean difference (*SMD*) with 95% confidence interval (*CI*), *p*-value, Chi-square (Chi^2), I^2 index, and the random-effects model. For the total effects of the lung functions, the two groups of herbs and acupuncture showed significant improvements; (n = 1041; *SMD* [95% *CI*] = 0.30 [0.18, 0.43], $p < 0.00001$) and (n =582; *SMD* [95% *CI*] = 0.41 [0.24,

0.59], $p < 0.00001$) respectively. The moxibustion group with one RCT did not provide significant improvement for the total lung functions of FEV1 and PEF but some positive result ($n = 554$; *SMD* [95% *CI*] = 0.16 [-0.01, 0.33], $p = 0.06$). This study suggested some positive evidences that the application of AOM as a complementary or alternative therapy to western treatment have a favorable effect for the improvement of lung functions on bronchial asthma. But for more precise estimate of treatments and less publication bias, are required more strictly processed clinical trials whether they were published or not.

Abbreviation: FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, and PEF = peak expiratory flow.

Key words: asthma, AOM, CAM, herbs, acupuncture, moxibustion, systematic review, meta-analysis, and RCT.

TABLE CONTENTS

I. INTRODUCTION

Asthma is a chronic inflammation of the airways of lungs characterized by reversible airway constriction, increased mucus production, and airway remodeling.[1,2] Main symptoms are wheezing, shortness of breath, coughing, and chest tightness.[3] These may occur few times a day or week and may become worse at night or with exercise.[1] Asthmatic patients had been increased significantly worldwide from 183 million in 1990 up to 358 million in 2015, and 397,100 people died of asthma mostly in the developing countries in 2015.[1,4-6] American Lung Association in May 2018 reported that more than 26 million Americans had asthma including 6.1 million children and the annual healthcare cost for asthma was approximately $56 billion, including indirect costs (e.g. lost productivity) of $5.9 billion.[7-9] Asthma is known to be caused by a combination of genetic and environmental factors such as air pollutions and allergens, and medications such as aspirin and beta brocker.[1,10] Diagnosis is mainly based on medical history, spirometry, and response to therapy overtime.[11]

There is no cure for asthma.[1] Though, most symptoms can be prevented by avoiding trigger (e.g. allergens and irritants), inhaled or oral corticosteroids (ICS or OCS), short or long-acting beta-2 agonists (SABA or LABA) such as salbutamol and salmeterol, leukotriene modifies, and theophylline.[12-16] Steroids, however, can suppress adrenal functions and immune systems, and increase the risk of respiratory infections.[17] Even beta-agonists can cause airway inflammation due to tolerance and actually increase the risk for asthmatic exacerbations.[18,19] It, thus, become further more necessary to develop novel approaches for the treatment of asthma. Moreover, roughly 50% of people with asthma, like those with other chronic disorders, use CAM therapies.[20,21]

AOM with a long history of more than 2,500 years is recently the major component of CAM in the world and still used as an alternative or complementary therapy to western medicine in Asian countries such as China, Korea, Japan, and India.[22-24] AOM has an independent system of theory, diagnosis, and treatment, in which the major modalities of treatment are herbs, acupuncture, and moxibustion.[25] From the perspective of AOM, asthma attack is an acute, excess condition, and caused by wind combined with cold or heat pathogenic factors, and between attacks, the body is considered to be in a deficient condition.[26] The lungs and kidneys play an important role cooperatively to produce wei qi (defensive qi), which can be regarded as the immune system and an energy that is manufactured by spleen from the food we intake.[26]

In FOCUS of Allergy Research Group (Summer/Fall 2017)[47], a formula called ASHMI (anti-asthma herbal medicine intervention) was introduced.[27] The formula is a blend of the three most effective herbs founded in a tradition 14-herb formula[28] with a long history of human use in China; Lingzi (*Ganoderma lucidum*), Gancao (*Glycyrrhiza uralensis*), and Kushen (*Sophora flavescens*). ASHMI has broad therapeutic effects on asthmatic inflammation and bronchoconstriction, and it also raises cortisol production instead of suppressing it as corticosteroid does. And while a steroid medication decreased the secretion of interferon-gamma, ASHMI increased it, regulating immune system.[27,28]

There is a number of indexes, approximately more than fifty, for asthma such as lung functions, quality of life and biomarkers in serum. But, indexes of quality of life are rather subjective than objective, and serum biomarkers are still controversial as mentioned above, while indexes of lung functions are accepted as objective and non-controversial. According to The Global Initiative for Asthma (GINA) report, the lung functions are most useful indicators of

further risk after diagnosis of asthma and particularly, FEV1 as a percentage of predicted is an important factor of the assessment of future risk.[40]

Objective of the Study

The objective of this study is to review systematically and analyze statistically the effect of AOM therapies of herbs, acupuncture, and moxibustion on bronchial asthma through the following process;

1. To collect literatures of Randomized Controlled Trials on bronchial asthma systematically.
2. To conduct the qualitative evaluation of Risk of Bias on RCT.
3. To extract outcome data of lung functions such as FEV1, FVC, FEV1/FVC, and PEF from the included studies, and to synthesize and evaluate through Meta-Analysis.
4. To analyze publication bias by the funnel plot.
5. To review and analyze the safety of AOM interventions on bronchial asthma.

II. METHODS

The reporting of the review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and recommendations of *PLoS Medicine* proposed in 2009.[29]

Search and Study Selection

The electric databases of PubMed, Cochrane Library, and EBS *host* were searched from October 2018 through May 2019, and the other relevant articles were further screened through the identified articles. The search terms were used as the following for compact results; (herbs OR acupuncture OR moxibustion) AND (asthma) AND (randomized controlled trial), and the included studies were categorized by clinical trials and recent 10 years in accordance with the guideline of PRISMA. Then, the titles and abstracts were screened for the full texts, which were finally screened for eligible studies.

Inclusion/Exclusion Criteria

The studies were included if they (were):

1. randomized controlled trials;
2. compared AOMs with western treatments;
3. included only asthmatic participants with a diagnosis of asthma;
4. included lung functions for outcome measures;

5. published in English between 2009 and 2019.

Trials with children, healthy controls, or animals were excluded.

Data Extraction and Items

Data were extracted using the predefined form from each eligible study. Its items are details of the first author, year, countries, sample size, age, severity of asthma, duration of intervention, experimental and control interventions, and outcome measures including lung functions, the follow-up period, and dose of interventions.

Risk of Bias within Individual Studies

For the methodological quality of the included studies, the risks of bias were assessed using the Cochrane Risk of Bias Assessment Tool.[30] It comprises seven quality elements:

1. Random sequence generation (selection bias);
2. Allocation concealment (selection bias);
3. Blinding of participants and personnel (performance bias);
4. Blinding of outcome assessment (detection bias);
5. Incomplete outcome data reporting (attrition bias);
6. Selective outcome reporting (reporting bias); and
7. Other bias.

Each item for risk of bias was given + (low risk of bias), ? (unclear), or – (high risk of bias).

Outcome Measure and Analyses

Outcome measures for the analysis of the review were pulmonary functions such as FEV1, FVC, FEV1/FVC, and PEF. RevMan 5.3 software for windows (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to perform the meta-analysis. All of the data in the review were continuous, and end-point scores were expressed as *SMD*s for different scales with associated 95% *CI*s. The random-effects model was assumed for combining data because the variation of the effects across studies can follow a particular distribution.[31] Chi^2 or I^2 statistic was used to evaluate heterogeneities of studies or lung functions where I^2 value of 50% or more is considered to be an index of substantial heterogeneity.[32]

Ethical Review

This systematic review was reviewed and determined as an exempt case from evaluation by Institutional Review Board of South Baylo University on November 29th, 2018.

III. RESULTS

Study Selection

A total of 190 citations was provided from PubMed, Cochrane Library, EBSCO, and other relevant sources at the first stage, and 86 articles remained for screening of titles and abstracts after adjusting for recent 10 years or clinical trials. Then, 37 studies were included for screening of full texts, and 7 studies were finally identified for the meta-analyses of the review. (**Figure 1**)

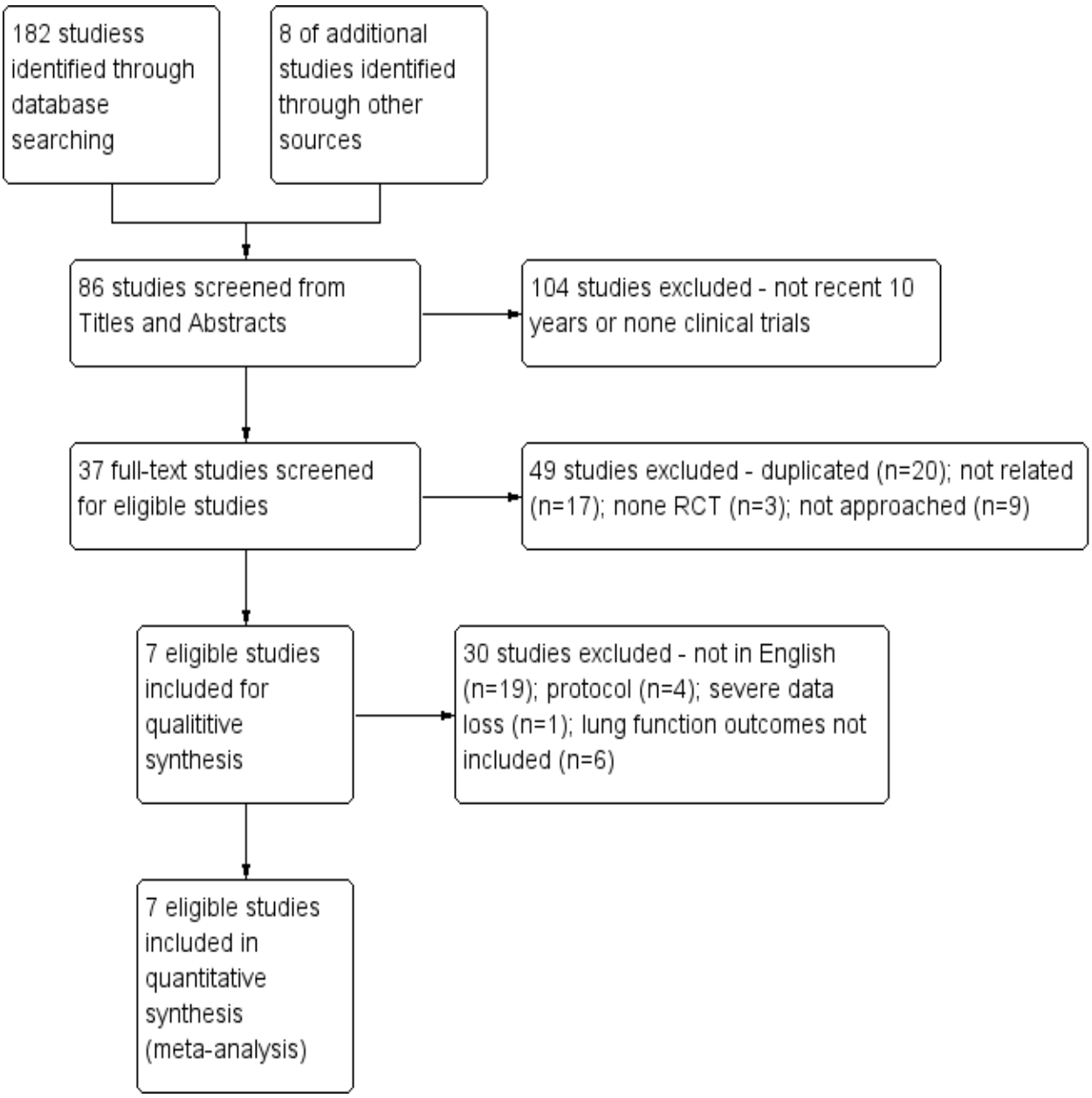

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram of Searching.

Study Characteristics

All seven studies[33-39] finally selected for the review included nine RCTs published in English between 2009 and 2019 years. There were five studies[33-35,37,39] with two arms, one study[38] with three arms, and one study[36] with two subgroups. The included trials involved 986 participants with mild, moderate, or severe asthma between 18 and 70 years old who were Chinese, Korean, Indian, and Turk, and only one study[35] included a severe case. The durations of the interventions were between one and three months, and four trials[35,38,39] reported the follow-ups. All of the trials had a run-in time as a single blind period before the randomization, and applied one modality of herbs, acupuncture, and moxibustion as an alternative or complementary therapy to western treatments, of which there were five trials[33-36] with herbs or herb formulas such as Loki zupa,[33] Ping Chuan Ke Li (PCKL),[34] Cordyceps sinensis,[35] and Curcumin,[36] three trials[37,38] with acupuncture applying acu-points of Ren 22, LU 5, ST 40, UB 13, LI 4, LU 9, LU 7, ST 36, LV 3, and Dingchuan, and one trial[39] with moxibustion at two horizontal lines of UB 13 and UB 17, and meanwhile, the interventions of control groups were ICS, LABA, Placebo, Sham acupuncture, or waiting. (**Table 1**)

Table 1. Characteristics of the nine included RCTs

Author (country)	Sample Age (min, max)	Duration Follow-up	Control Groups	Experimental Groups	Main Outcome Measures
Lv[33] (China)	n=218 (18, 70)	8 weeks __	[a]ICS + Placebo.	ICS+[a]Loki zupa 3*10ml/day.	[b]FEV1,FEV1/[b]FVC, [b]PEF, [c]ACT, [c]AQLQ,[d]IL-2,4,5,10,13,17,33, [d]IFN-gamma, [d]TGF-beta.
Wang[34] (China)	n=72 (18, 60)	3 months __	Montelukast; 10 mg/day. +Placebo.	+[a]PCKL; 3*20g.	FEV1, FEV1/FVC, and [c]SGRQ.
Wang[35] (China)	n=120 (18, -)	3 months 3 months	ICS and [a]LABA in need.	+ [a]Cordyceps ;3*1.2g/day.	FEV1, FEV1/FVC, PEF, AQLQ, [d]Ig G, Ig E, [d]ICAM-1, IL 4 IFN-gamma, [d]MMP-9.
Abidi-1[36] (India)	n=60 (18, 55)	1 month __	Routine therapy.	+Curcumin ; 500mg/day.	FEV1, [d]ESR.
Abidi-2[36] (India)	n=60 (18, 55)	1 month __	Routine therapy.	+Curcumin ; 500mg/day.	[b]post-bronchodilator FEV1.
Bilgin[37] (Turkey)	n= 120 (20, 70)	10 sessions __	Sham	acupuncture;LI4, LU9,LU7,ST36,LV3.	FEV1,FVC, FEV1/FVC PEF, [b]FEF 25-75.
Choi-1[38] (Korea)	n=29 (19, 70)	4 weeks 2 weeks	Sham	acupuncture;LU5, Ren22, ST40,UB13.	FEV1, PEF, lg E [c]QLQAKA, [c]TDI.

Table 1. - *continued*

Author (country)	Sample Age (min, max)	Duration Follow-up	Control Groups	Experimental Groups	Outcome Measures
Choi-2[38] (Korea)	n=29 (19, 70)	4 weeks 2 weeks	Waiting	acupuncture; LU5, Ren22, ST40,UB13	FEV1, PEF, lg E QLQAKA, TDI
Chen[39] (China)	n=277 (18, 65)	3 months 3 months	Seretide ;twice a day	Moxibustion at two horizontal lines of UB13 and UB17	FEV1, PEF, ACT

[a]**Interventions;** ICS (inhaled corticosteroid), LABA (long-acting beta-agonist), Loki zupa; Shenxiangcao (Boriss), Yuanweigen (Iris halophilia pal), and Honey, PCKL (Ping Chuan Ke Li),[44,45] Cordyceps sinensis; Corbrin capsule, Hangzhou Huadong Pharmaceutical Co. Ltd. [b]**Lung Function Tests;**[42] FEV1 (forced expiratory volumes in one second), FVC (forced vital capacity), PEF (peak expiratory flow), FEF25-75 (forced expiratory flow 25-75%), post-bronchodilator FEV1 (assessed at 20 minutes after inhalation of 200 ug Salbutamol). [c]**Quality of Life Questionnaires;** AQLQ (the Juniper's Asthma Quality of Life Questionnaire),[41] SGRQ (St George's Respiratory Questionnaire),[46] ACT (asthma control test), QLQAKA (quality of life questionnaire for adult Korean asthmatics), TDI (transition dyspnea index). [d]**Biomarkers in Serum;**[43] IL (interleukin), Ig (immunoglobulin), ESR (erythrocyte sedimentation rate), ICAM (intercellular adhesion molecule), IFN (interferon), MMP (matrixmetalloproteinase), TGF (transforming growth factor).

Risk of Bias within the Included Studies

All but one study[36] conducted the randomization sequence using computer systems, random sampling numbers, or a simple randomization method. Only three studies[33,34,39] concealed allocations through sealed envelopes or a central randomization. Selective outcome reporting bias were not detected from five studies,[33,35,37-39] and two studies[34,36] did not provide sufficient information to judge it. Three studies[33,34,38] used a double-blind method, and one study[37] conducted a single blind method on the performance. Four studies[33,34,38,39] were blinded to assess

outcomes, but the rest did not describe sufficient details about that. All of the included studies, applying the intention-to-treat (ITT) principle (Appendix) completed handling of incomplete outcomes, and were unlikely to have produced an attrition bias. (**Figure 2, 3**)

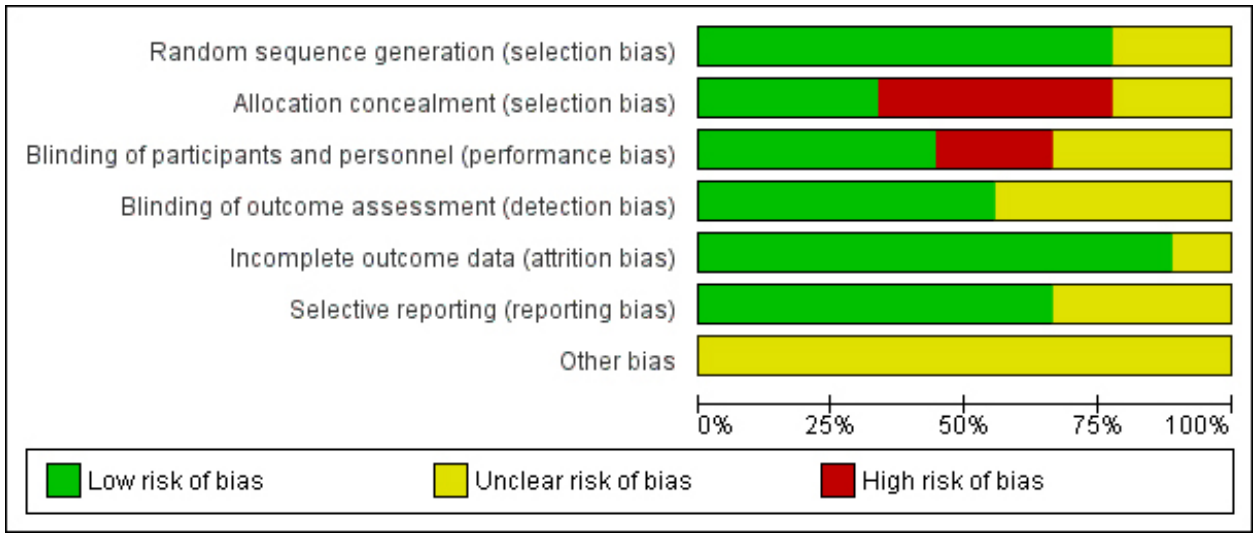

Figure 2. Risk of Bias on Each Item across All the Included Studies with Percentages.

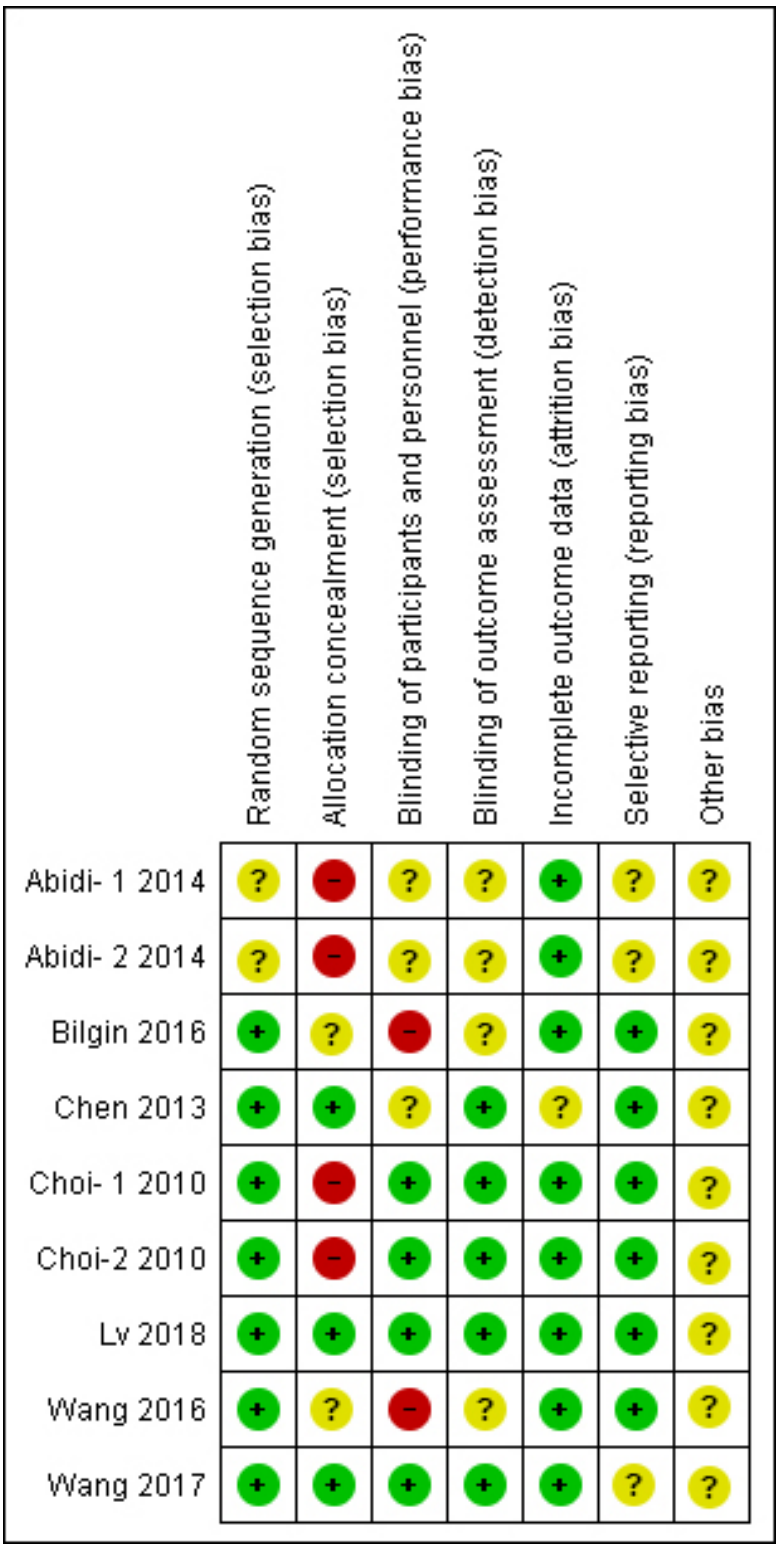

Figure 3. Risk of Bias within the Included Studies.

Outcome Measures

The outcomes of the included trials were summarized based on the following three categories; herbs versus western treatments, acupuncture versus western treatments, and moxibustion versus western treatments.

Herbs versus Western treatments

For the group of herbs with four studies[33-36] of five trials, a total of lung functions (FEV1, FEV1/FVC, and PEF), FEV1, and PEF were improved significantly compared to the group of western treatments with low heterogeneity among studies: (n = 1041; *SMD* [95% *CI*] = 0.30 [0.18, 0.43], $p < 0.00001$; $Chi^2 = 5.74$, $df = 8$ ($p = 0.68$), $I^2 = 0\%$), (n = 475; *SMD* [95% *CI*] = 0.32 [0.14, 0.50], $p = 0.0006$; $Chi^2 = 1.77$, $df = 4$ ($p = 0.78$), $I^2 = 0\%$), and (n = 283; *SMD* [95% *CI*] = 0.40 [0.16, 0.63], $p = 0.0009$; $Chi^2 = 0.21$, $df = 1$ (p =0.64), $I^2 = 0\%$) respectively. Although *SMD* of FEV1/FVC recorded 0.20, it was not statistically significant with 54% of heterogeneity of studies (n = 283; *SMD* [95% *CI*] = 0.20 [-0.15, 0.55], $p = 0.25$; $Chi^2 = 2.18$, df = 1 ($p = 0.14$), $I^2 = 54\%$). (**Figure 4**)

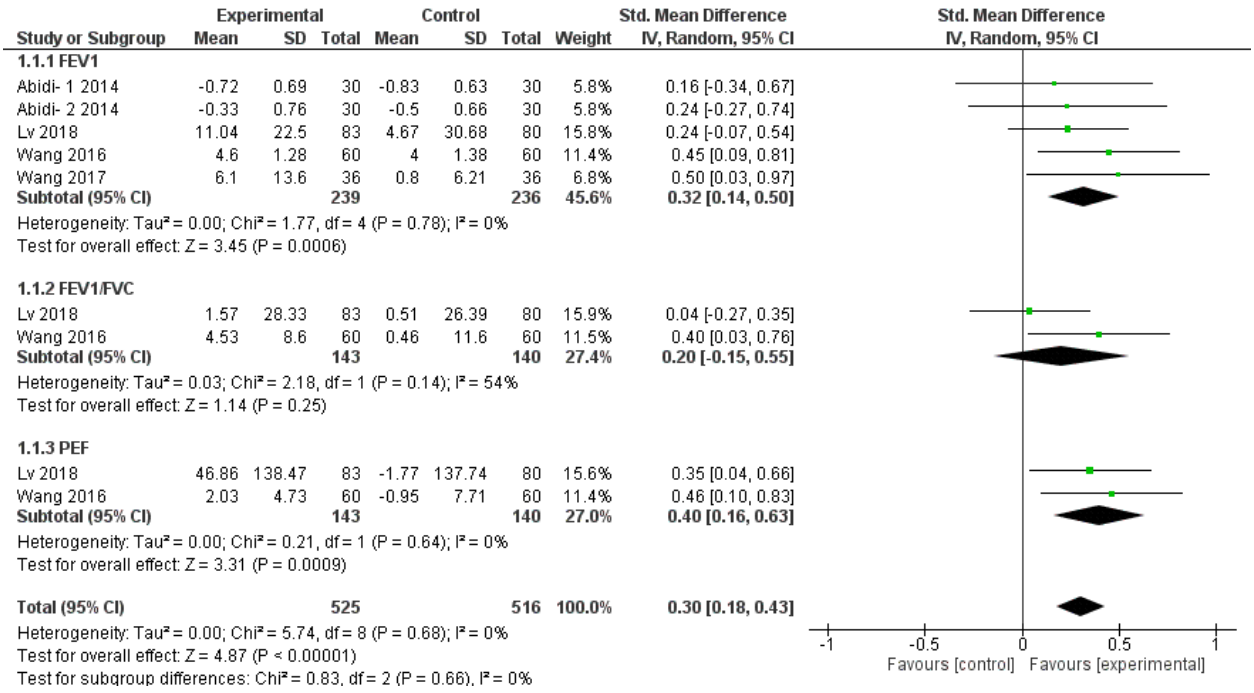

Figure 4. Forest Plot of Effects of Herbs versus Western Treatments on Lung Functions of FEV1, FEV1/FVC, and PEF.

Acupuncture versus Western treatments

At the acupuncture group with two studies[37,38] of three trials, an aggregated effect of pulmonary functions (FEV1, FVC, FEV1/FVC, and PEF), FVC, FEV1/FVC suggested good results with low heterogeneity of studies: (n = 582; *SMD* [95% *CI*] = 0.41 [0.24, 0.59] $p <$ 0.00001; Chi^2 = 7.37, df = 7 (p = 0.39), I^2 = 5%), (n = 120; *SMD* [95% *CI*] = 0.59 [0.22, 0.95], p = 0.002), and (n = 120; *SMD* [95% *CI*] = 0.55 [0.18, 0.91], p = 0.003) in order. FEV1 and PEF showed some improvable aspect, but were not statistically significant: FEV1 (n = 171; *SMD* [95% *CI*] = 0.23 [-0.07, 0.53], p = 0.14; Chi^2 = 1.54, df = 2 (p = 0.46), I^2 = 0%) and PEF (n = 171; *SMD* [95% *CI*] = 0.33 [-0.09, 0.75], p = 0.13; Chi^2 = 2.98, df = 2 (p = 0.23), I^2 = 33%).

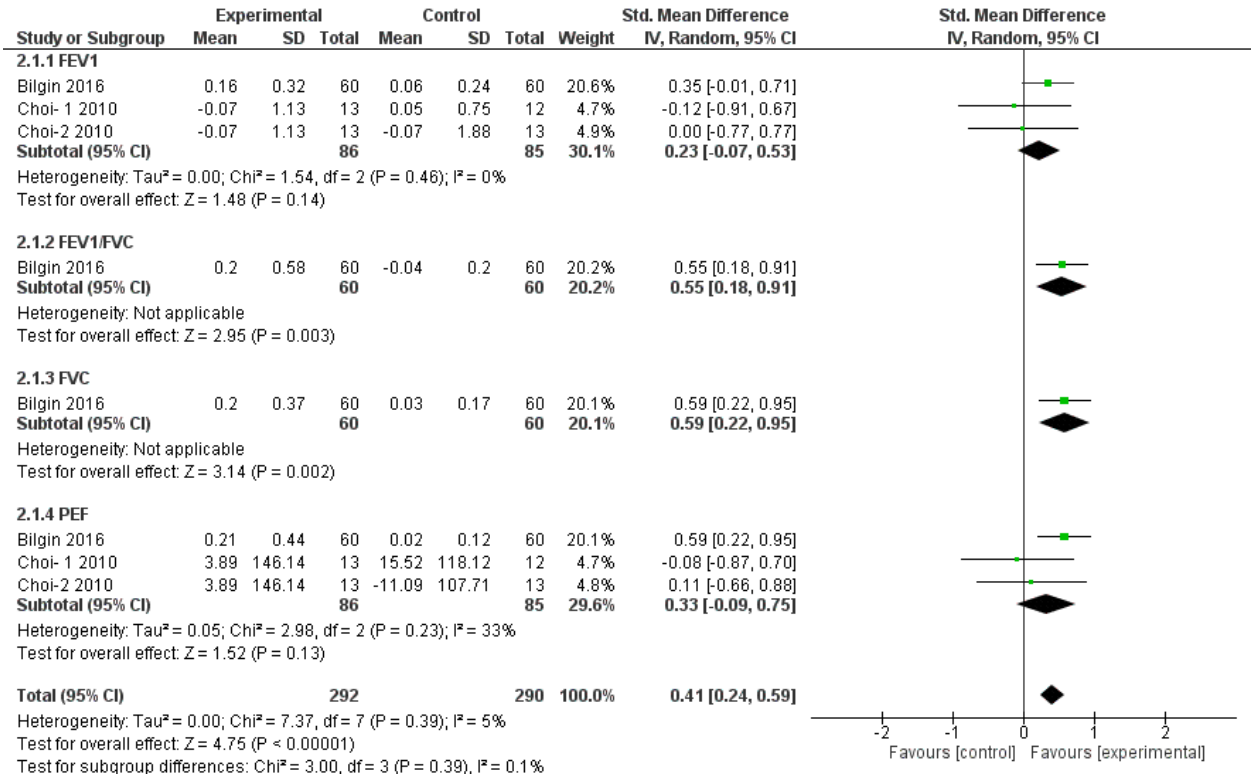

Figure 5. Forest Plot of Effects of Acupuncture versus Western Treatments on Lung Functions of FEV1, FEV1/FVC, FVC, and PEF.

Moxibustion versus Western treatment:

This group with one trial[39] involving 277 participants did not provided statistical significance, but showed some improvable effect: a total of FEV1 and PEF (n = 554; *SMD* [95% *CI*] = 0.16 [-0.01, 0.33], p = 0.06; Chi^2 = 0.01, df = 1 (p = 0.94), I^2 = 0%), FEV1 (n = 277; *SMD* [95% *CI*] = 0.15 [-0.08, 0.39], p = 0.20), and PEF (n = 277; *SMD* [95% *CI*] = 0.17 [-0.07, 0.40], p = 0.17). (**Figure 6**)

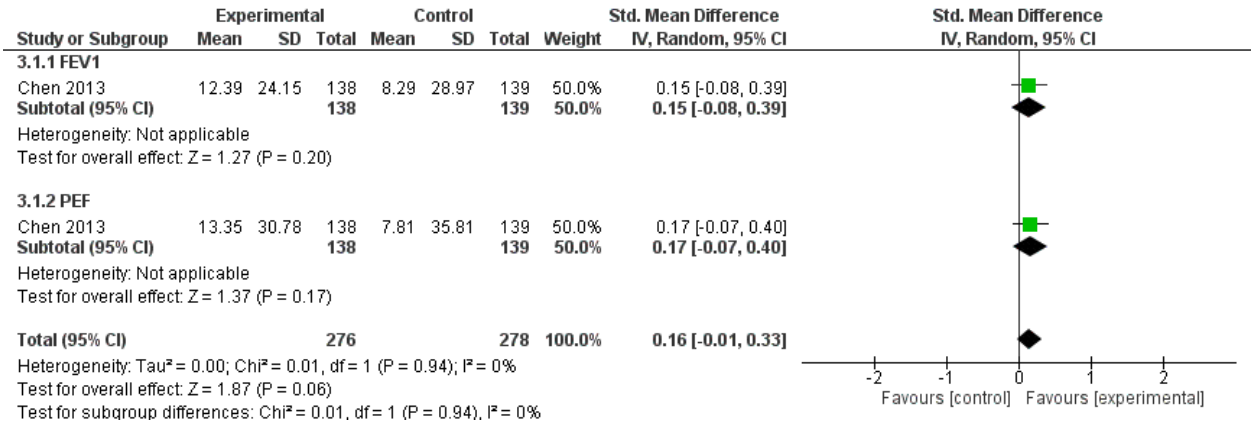

Figure 6. Forest Plot of Effects of Moxibustion versus Western Treatments on FEV1 and PEF.

Sensitivity Analyses

According to results of sensitivity analyses on three categories of herbs, acupuncture, and moxibustion, all of the three categories included possibilities of publication bias; the herbs group with one outlier and moderate asymmetry in the middle, (**Figure 7)** the acupuncture group with severe asymmetry of the small positive studies in the bottom and the large negative studies over the middle being missing, (**Figure 8)** and the moxibustion group with perfect symmetry but just two studies. (**Figure 9)**

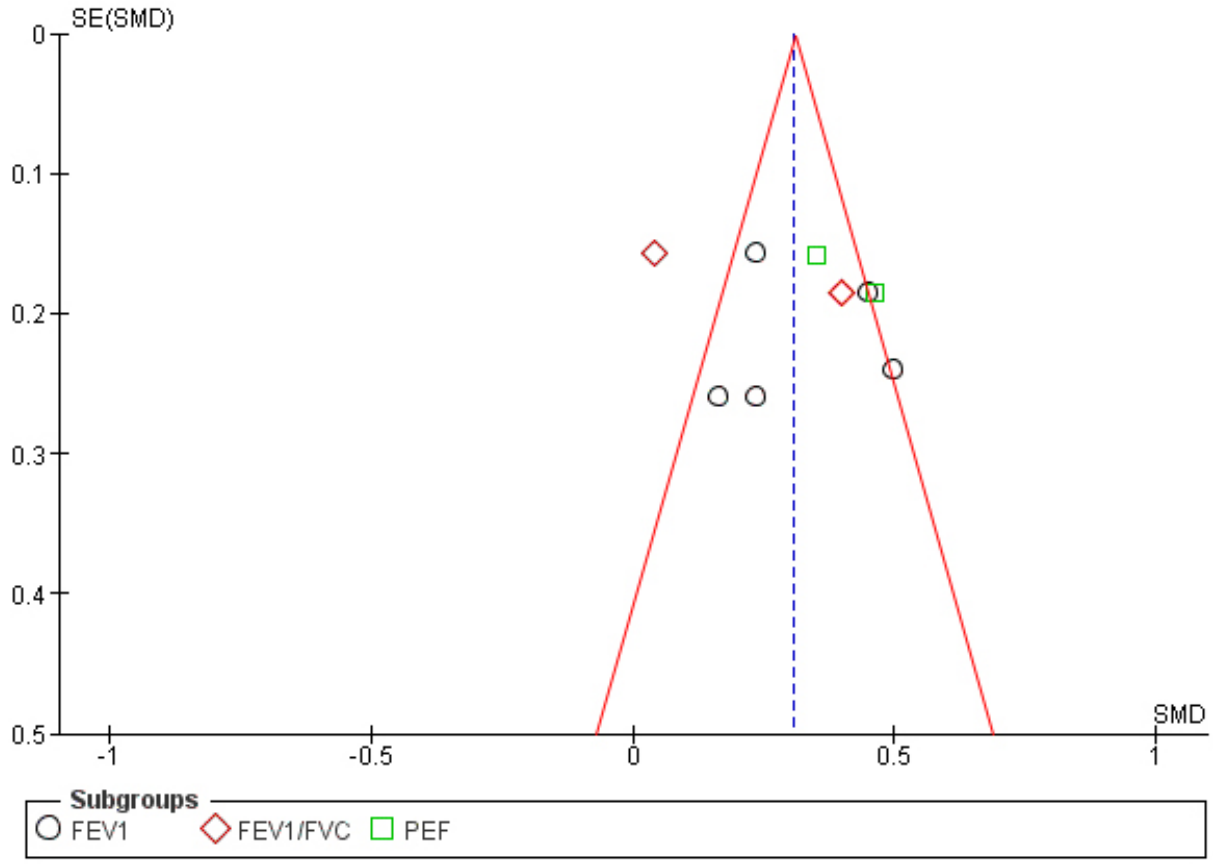

Figure 7. Funnel Plot of Studies Included in the Herbs Group.

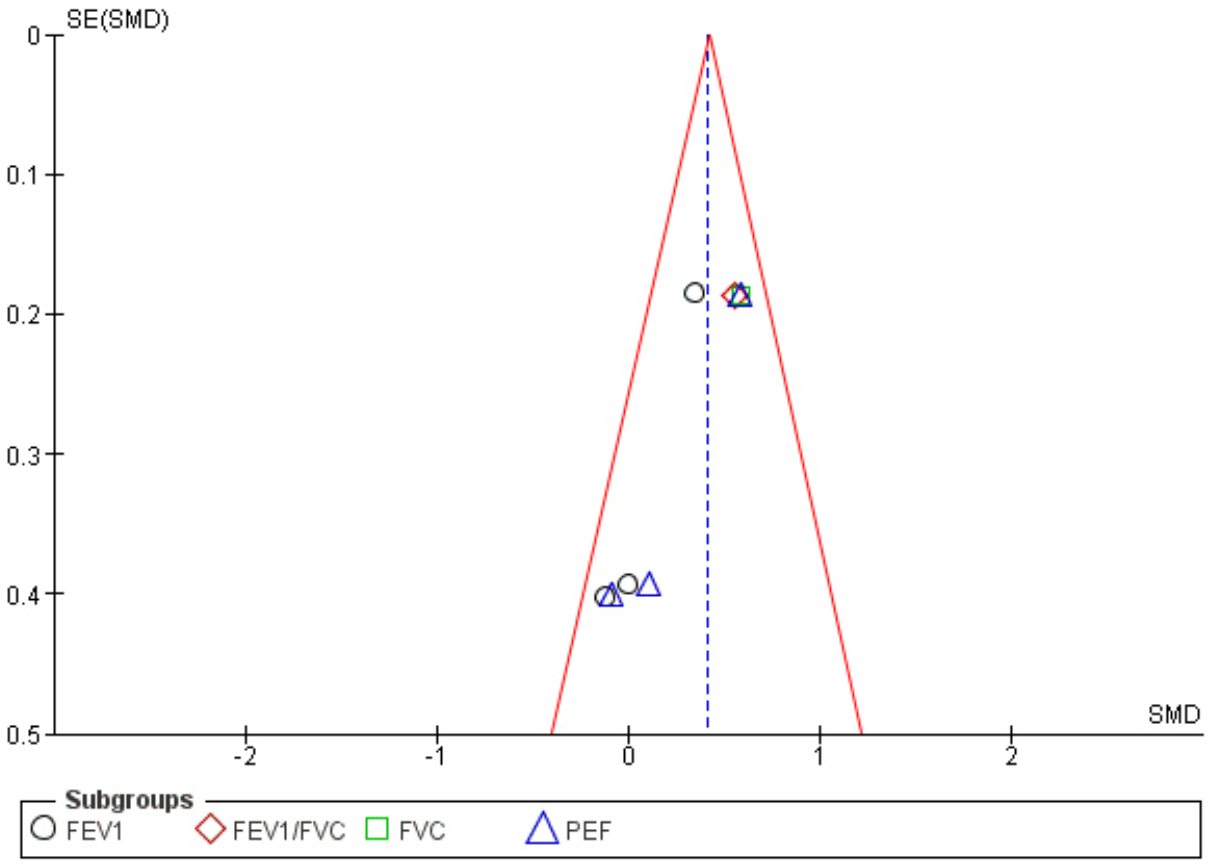

Figure 8. Funnel Plot of Studies Included in the Acupuncture Group.

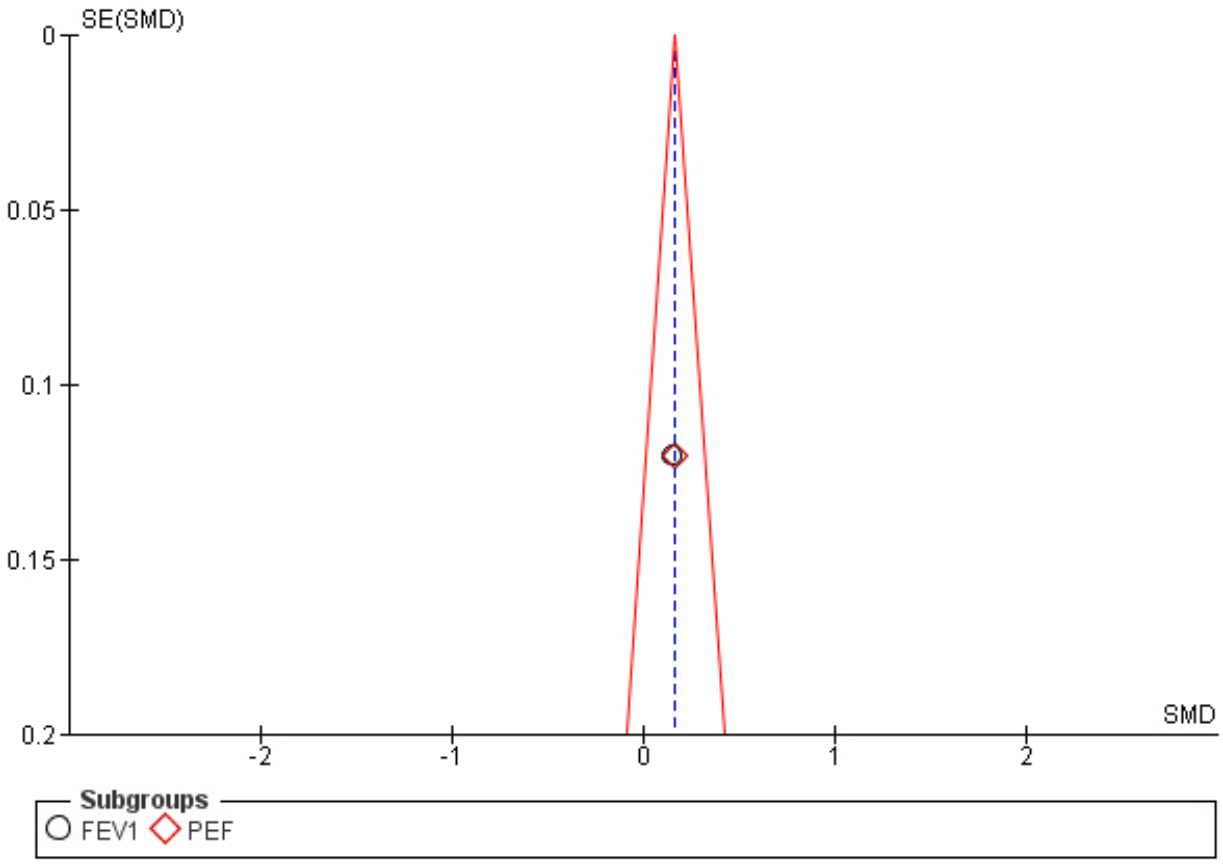

Figure 9. Funnel Plot of Studies Included in the Moxibustion Group.

Subgroup Analyses

Tests for the subgroup differences of pulmonary functions such as FEV1, FVC, FEV1/FVC, and PEF showed good consistencies at all of the three categories; herbs group ($Chi^2 = 0.83$, $df = 2$ ($p = 0.66$), $I^2 = 0\%$), acupuncture group ($Chi^2 = 3.00$, $df = 3$ ($p = 0.39$), $I^2 = 0.1\%$), and moxibustion group ($Chi^2 = 0.01$, $df = 1$ ($p = 0.94$), $I^2 = 0\%$).

Safety

All of the included studies but one[37] reported adverse events (AEs) which were mild or not; Lv 2018[33] with non-AE, Wang 2017[34] with nausea (13.8%: 8.3%) and (8.3%: 11.1%) in both groups (experimental: control), Wang 2016[35] with headache, throat discomfort, and dry mouth in 10% of experimental group and 13% of control group, Abidi 2014[36] with weight gain in experimental group and poor appetite in control group, and headache and insomnia in both groups, Choi 2010[38] with nausea and dizziness, and Chen 2013[39] with 5 cases of headache and 4 cases of palpitation.

IV. DISCUSSION

In this review, seven studies[33-39] of nine RCTs involving 986 patients with asthma were included in meta-analyses to investigate the effect of AOM on bronchial asthma. The experiment was conducted for three groups of herbs, acupuncture, and moxibustion compared to western treatments. Overall, findings of the review suggested that AOM therapies had beneficial effects on bronchial asthma. The herbs group[33-36] showed significant improvements for a total of pulmonary functions ($p < 0.00001$), FEV1 ($p = 0.0006$), and PEF ($p = 0.0009$), but did not for FEV1/FVC ($p = 0.14$). In the acupuncture group[37,38] a total of lung functions ($p < 0.00001$), FEV1/FVC ($p = 0.003$), and FVC ($p = 0.002$) were statistically significant, but FEV1 ($p =0.14$) and PEF ($p = 0.13$) were not. The moxibustion group with one trial of 277 participants provided some positive measures but with none significance ($p = 0.06$).

Asthma is a chronic, inflammatory disease of the airways sometimes with asthmatic exacerbations of life threatening.[1,2] Today, there is no treatment for asthma.[1] The majority of asthmatic patients take medications such as ICS and LABA to maintain the functions of the airways. In asthma attacks, quick-acting medications or emergency treatments may be helpful for the patients.[12-16] But for long term treatments of asthma, they should beware of some systemic side effects of western medications for asthma, which can suppress adrenal functions, lead to tolerance, or actually cause airway inflammation.[17,18]

AOM therapies including herbs, acupuncture, and moxibustion with a long history over 2500 years have been applied for asthma treatments as an alternative or complementary therapy to

conventional treatments using western medications.[22-24] Moreover, AOM modalities in this study showed some positive effects on lung functions of patients with asthma.

Limitations

There were several limitations in the review. First, the achieved effects in the review were not the results of AOM alone, but with western medications. Second, the studies for children were not included because it is difficult to test their pulmonary functions. Third, the included studies were published in English for recent 10 years since the development of PRISMA. Finally, it was not possible to personally access some databases without institutions registered in them.

V. CONCLUSION

This study showed statistical evidences that on bronchial asthma, AOM therapies can improve some lung functions such as FEV1 (p =0.0006) and PEF (p = 0.0009) in the herbs group, and FVC (p = 0.002) and FEV1/FVC (p = 0.003) in the acupuncture group through regulating immune functions instead of suppressing them unlikely western medications, and so, could reduce frequencies of asthmatic exacerbations and dosages of medications with adverse effects. But According to the sensitivity analyses of publication on studies included in this experiment, all the three groups of herbs, acupuncture, and moxibustion included possibilities of publication bias such as outliers and asymmetries indicating the loss of negative or positive studies. Thus, to make precise decisions for the effectiveness of AOM on bronchial asthma, are required adjusting of studies included in meta-analyses of the review through trimming of outliers and filling the loss of negative or positive studies and more strictly designed clinical trials whether are published or not.

If one has a bronchial asthma and is willing to get AOM therapies as CAM to western medicines, it's highly recommended to carefully consult a licensed acupuncturist including respiratory specialists such as an immunologist, allergist, or pulmonologist.

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APPENDIX

The intention-to- treat (ITT) principle:

The ITT population is defined as the randomized participants. The data analyses of baseline characteristics were based on the ITT population as well as the primary and secondary indexes. In the ITT population, none of the participants are excluded and the participants are analyzed according to the randomization scheme. The basic ITT rule is that participants in the trials should be analyzed, regardless of whether they receive or adhere to treatment.