

## The impact of reflexology and homeopathy added to conventional asthma treatment on markers of airway inflammation – a randomised study

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### ABSTRACT

**Background:** Asthma is a common chronic airway disease associated with hyperresponsiveness and airway inflammation. Anti-inflammatory medication especially inhaled corticosteroids are important for control of airway inflammation, decrease of airway hyperresponsiveness and lung function variability, reduce asthma symptoms, and improve lung function as well as quality of life. Most studies investigating the influence of complementary and alternative medicine (CAM) in asthma measure clinical effectiveness, but only few evaluate the impact on markers of airway inflammation.

**Objective:** The aim of this study was to investigate the effect of reflexology and homeopathy added to conventional treatment on different markers of airway inflammation in asthma.

**Methods:** Eighty-four patients with asthma were randomized to receive conventional treatment alone or conventional treatment with addition of homeopathy or reflexology in a single center, investigator blinded, controlled, one-year trial. During the study period, patients regularly consulted their general practitioner for evaluation and asthma treatment. At randomization, and after 6 and 12 months, methacholine challenge test and measurement of exhaled nitric oxide were performed. Blood samples were collected for eosinophil count and measurement of serum eosinophil cationic protein.

**Results:** No significant differences between groups for any of the inflammatory markers were demonstrated. Methacholine responsiveness improved in all three groups but improvements were not statistically significant within and between groups.

**Conclusions:** This randomized controlled study of reflexology and homeopathy failed to show significant improvement on selected markers of inflammation and airway hyperresponsiveness in asthma.

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Complementary and alternative medicine; reflexology; homeopathy; asthma; randomized controlled trial; inflammation

## Introduction

Asthma is a common disease and estimated to affect 300 million people worldwide. Asthma is associated with a mononuclear and eosinophilic airway inflammation and bronchial hyperresponsiveness (BHR). Inhaled corticosteroids are the most effective anti-inflammatory medications in asthma treatment [1]. However, currently, there is no medication available that can cure asthma. This may be one of the possible explanations why patients with asthma expect benefit from complementary and alternative medicine (CAM) that have totally different explanations for asthma pathogenesis and treatment compared to the established medical tradition.

Although patient reported outcomes are important markers for evaluating clinical manifestations of asthma, patients' positive, subjective experience as

a result of alternative therapy gives no solid evidence for a clinical effect of CAM treatment. Wechsler et al. compared the effects of the bronchodilator, two placebo interventions (sham acupuncture and a placebo inhaler) and no intervention on outcomes in patients with asthma [2]. Lung function test improved only in the group treated with bronchodilator. However, patients' reports of improvement after intervention did not differ significantly between bronchodilator and placebo intervention but the subjective improvement with all three interventions was significantly greater than that with the non-intervention control. Result shows that placebo effects influence subjective outcomes and self-report of improvement can be unreliable in assessing asthma control. Therefore, using biomarkers and evaluation of BHR in clinical trials

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with asthma will allow for more rigorous testing of the interventions and to identify poor asthma control and future risk of exacerbation.

Studies have demonstrated that the number of eosinophils in blood, serum eosinophil cationic protein (s-ECP) and exhaled nitric oxide (FeNO) are sensitive indicators of disease activity in asthma [3–5]. In addition, BHR is an indirect measure of inflammation and can be monitored by inhalation challenge tests. These tests provide information about severity of airway reactivity and mucosal inflammation [6,7].

Homeopathy and reflexology are the most commonly used CAM therapies in asthma [8,9]. The exact mechanism of action of these therapies is not known. The effect of homeopathy and reflexology in asthma treatment has been investigated in earlier studies. The vast majority of these studies assessed symptoms, quality of life and lung function [10–12]. Only a few studies have assessed the effect on airway inflammation of homeopathy in asthma [13–15].

The observed anti-inflammatory benefit from earlier studies can support the evidence of potential anti-inflammatory effect of homeopathy and reflexology. However, studies with unclear or inadequate methodological quality may be associated with risk of bias compared with trials using adequate methods, possibly leading to overestimation of intervention benefits.

The aim of the present study was to test the hypothesis that homeopathy and reflexology would lower selected markers of airway inflammation and BHR in patients with asthma in an investigator-blinded, randomized, controlled, parallel group study design during a 1 year follow-up period.

## Methods

### Study design

This was a single-center, randomized, investigator blinded, controlled, parallel-group study design. The study was conducted in accordance with ethical principle of the Declaration of Helsinki and to the guidelines of *Good Clinical Practice*. All subjects provided written informed consent before participating in any study-related procedures. The study was approved by the Aarhus County Committee on Biomedical Research Ethics and the Danish Data Protection Agency. The study was monitored by the Unit for ‘Good Clinical Practice’ at Aarhus University Hospital. A steering committee including representatives from the Danish Reflexology Association, the Danish Society of Classical Homeopaths and the clinical research site was involved in the elaboration of the study protocol and agreed on

the protocol efficacy and safety outcomes. This committee met regularly before, during and after the study.

Following a two-week run-in period, eligible patients were randomized to receive either: conventional treatment alone, conventional treatment plus reflexology or conventional treatment plus homeopathy. Treatments were continued for 52 weeks, with assessments at baseline, at week 26 and week 52 (Figure 1).

### Patients

Patients were eligible if they were at least 18 years of age and had a history of bronchial asthma for a minimum of 6 months prior to baseline. Inclusion criteria were as follows: forced expiratory volume in 1 second ( $FEV_1$ )  $\geq 60\%$  predicted before bronchodilator and an objective measure of abnormal variation in bronchial caliber [1]. The objective measure was fulfilled if at least one of the following: 1) a positive reversibility test, defined as increase in  $FEV_1 \geq 10\%$  after inhalation of 400  $\mu\text{g}$  salbutamol; 2) a positive methacholine test, defined as a PD<sub>20</sub> of  $<1000 \mu\text{g}/\text{ml}$ ; 3) a positive test for exercise-induced asthma defined as a fall in  $FEV_1 > 15\%$  after a standardized 6-min exercise test; and 4) a positive peak expiratory flow (PEF) variability, defined as  $\geq 3$  days or 2 consecutive days with a difference between morning and evening PEF of  $>20\%$  during a 2-week period.

We excluded patients if they had been hospitalized for asthma within the past 3 months, or if they had an asthma exacerbation during the last month. Other exclusion criteria were changes in asthma medication within 30 days from screening and a smoking history  $>10$  pack-years.

All patients were allowed to use any kind of asthma medication during the study (inhaled and oral  $\beta_2$  agonist, inhaled and oral steroids, leukotriene receptor antagonists, theophyllines, anticholinergics, chromones).

### Visit schedule

Baseline visit took place for those who met the inclusion/exclusion criteria. During this visit, investigator recorded history of asthma and total medication score. Medication score for inhaled corticosteroids was calculated by converting inhaled corticosteroid doses to beclomethasone dipropionate equivalent doses (1 point: inhaled corticosteroid (ICS)  $\leq 500 \mu\text{g}$ , 2 points:  $501 \mu\text{g} \leq \text{ICS} \leq 1000 \mu\text{g}$ , 3 points:  $1001 \mu\text{g} \leq \text{ICS} < 2000 \mu\text{g}$ , 4 points  $>2000 \mu\text{g}$ , 5 points: oral steroid). One point for each of the following medications was given: short-acting  $\beta_2$ -agonist, long-acting  $\beta_2$ -agonist, leukotriene modifier, theophylline,

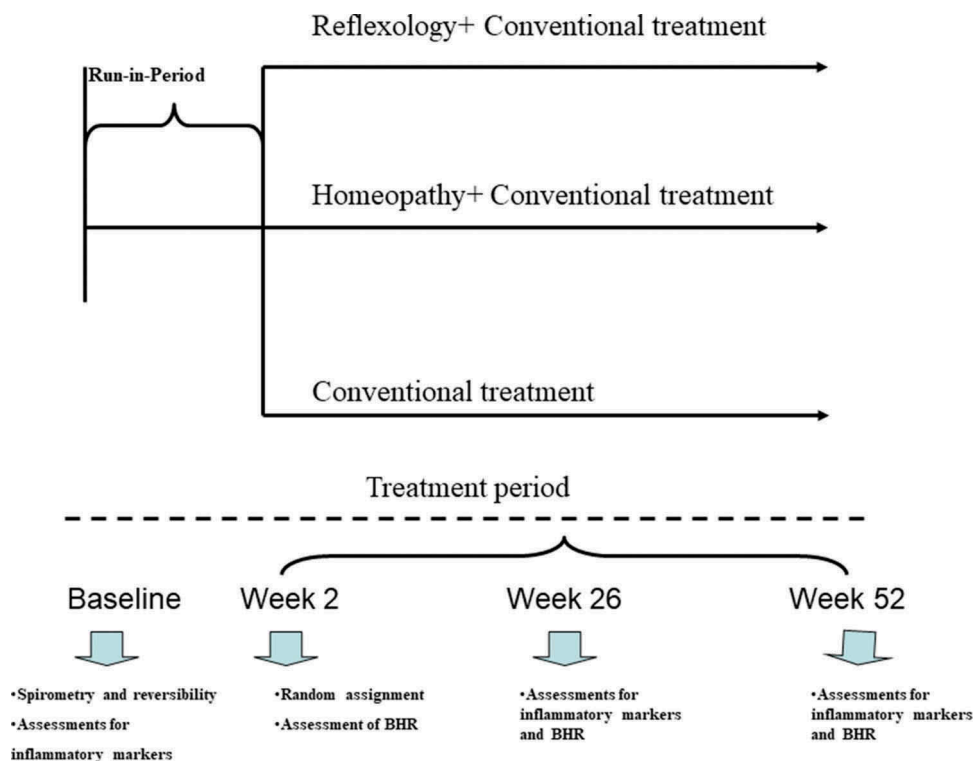


Figure 1. Study flow chart.

inhaled short- and long-acting anticholinergic. All individual scores were summed for a total score which could range from zero to ten.

Spirometry and blood samples for analysis of specific IgE to common inhalant allergens, eosinophils and s-ECP were obtained from all patients. Exhaled NO was also analyzed. Symptom and PEF were monitored during the 2 weeks run-in period. At the end of the run-in period, eligible patients were randomized to one of three groups: conventional treatment alone, conventional treatment plus reflexology or conventional treatment plus homeopathy. BHR was assessed using methacholine challenge testing at randomization. During the visit at week 26, measurements of FeNO, spirometry with reversibility testing and total medication score were determined. Blood samples were drawn for eosinophil count and measurement of s-ECP. Methacholine challenge test was performed on a separate day (1–4 days after the described visit). All assessments were repeated after 52 weeks treatment.

### Interventions

Reflexology and homeopathic treatments were given in addition to patients' current asthma treatment. Homeopathic treatment was based on principles for classical homeopathy and performed on an individual

basis by the homeopath from the Danish Society of Classical Homeopathy. Patients received homeopathic product with potency between C30 (dilution by a factor  $100^{30} = 10^{60}$ ) and M10 (dilution by a factor  $1000^{10} = 10^{30}$ ). Patients attended six to twelve homeopathy sessions and the number was decided by the homeopath on an individual basis.

Reflexology was performed by two reflexologists recommended by the Danish Reflexology Association. Duration of treatment and the number of sessions were individualized at the discretion of the reflexologist.

All patients received usual care of asthma from their general practitioner who monitored and adjusted treatment during the study period.

### Outcome parameters

Outcome parameters were the changes in markers of inflammation, i.e. eosinophil blood count, s-ECP and F<sub>e</sub>NO from baseline to week 26 and week 52. Changes from baseline in BHR were also assessed with methacholine challenge test after 26 and 52 weeks.

### Exhaled NO

F<sub>e</sub>NO measurement was carried out in accordance with the current international guidelines using a NIOX MINO Airway Inflammation Monitor (Aerocrine AB,

Solna, Sweden) [16]. F<sub>e</sub>NO measurements were performed prior to spirometry. In brief, patients inhaled to total lung capacity through the NIOX MINO and subsequently exhaled for 10 s at 50 ml/s. The mean of three acceptable measurements was recorded. The upper limit of NO for healthy adults was considered as 25 parts per billion (ppb) [17].

### **Serum ECP**

Measurement of s-ECP was done after allowing venous blood to clot for 60 min at 20°C, followed by centrifugation (10 min, 4°C, 1600g). The serum samples were kept at – 80°C until analysis. S-ECP was measured by Pharmacia CAP System® ECP fluorescence-emission immunoassay (Pharmacia&Upjohn Diagnostics AB, Uppsala, Sweden) according to the instructions of the manufacturer. The detection limit was 0.5µg/l.

### **Blood eosinophils**

Blood eosinophil counts were determined using the Sysmex XE-5000 automated analyzer (Sysmex Corporation, Japan).

### **Atopic status**

Patients were tested for specific sensitization to inhalant allergens by serum measurement of specific IgE (ImmunoCAP system, Pharmacia&Upjohn Diagnostics AB, Uppsala, Sweden). The six inhaled allergens tested were dog, cat dander, house dust mite, grass, mugwort and birch pollen.

### **Bronchial hyperresponsiveness**

Methacholine challenge tests were done at randomization, week 26 and week 52. All patients were informed to avoid the following medications before the test: short-acting inhaled bronchodilators (8 h), long-acting inhaled bronchodilators and leukotriene modifier (24 h), cetirizine (3 days). The dosimeter method was applied using Spira Elektro II (Respiratory Care Center, Hameenlinna, Finland) [18]. The patient was instructed in tidal breathing through a mouth piece (inspiratory flow 0.5 L/s, inspiratory volume 500–800 ml). Baseline FEV<sub>1</sub> was determined 90 s after six inhalations of saline. Afterwards, methacholine was administered in doubling doses from 18 to 11520 µg. The test was terminated when a decrease in FEV<sub>1</sub> from baseline of 20% or greater was observed, and PD<sub>20</sub> was calculated by interpolation of the cumulative dose from the response curve.

## **Statistics**

### **Randomization**

Randomization was performed using computer-generated block randomization (12 per block). Treatment allocation codes were given to patient by a member of the clinic staff, who was not involved in the study otherwise. Afterwards, patients were referred to the relevant therapist. All the staff, involved in evaluations and tests of patients was unaware of treatment allocations at all times. Patients were advised not to reveal their group allocation to the staff and investigators.

### **Sample size and statistical analysis**

Primary and secondary outcome parameters from the study have been reported previously [19]. The number of patients needed for the study was based on the Asthma Quality of Life Questionnaire (AQLQ) as the primary outcome variable. However, markers of airway inflammation were evaluated as predictors of treatment effects and sample size was not prespecified in the study protocol. Exploratory analyses of responses to treatments according to inflammatory markers were performed using data from the study.

All statistical analyses were performed using the intention to treat (ITT) population which included all subjects who were randomized to treatment and took at least one-treatment session. Missing values were imputed using the last observation carried forward method. Since the exploratory nature of this study, a power calculation for sample size was not performed.

Data were analyzed by Intercooled Stata (version 11, Stata Corporation, Collage Station, Tx, USA). Data were presented as mean (CI) when variables were normally distributed. Variables with skewed distribution were log transformed and reported as geometric means and CI. We used an analysis of variance (ANOVA) model to estimate treatment group means and between-group differences.

## **Result**

### **Study population**

One hundred eighty-seven participants were screened. Of these, 98 patients were eligible according to the inclusion and exclusion criteria. Absence of an objective measure of abnormal variation in bronchial caliber was the most frequent reason for ineligibility.

In total, 84 patients were randomly assigned one of the three treatment groups. During the study, 14 patients dropped out (reflexology n = 4, homeopathy n = 6, conventional treatment n = 4). Data from 84 patients were included in the statistical analysis (Figure 2).

Demographic and asthma characteristics of the subjects at baseline are listed in [Table 1](#). No significant differences were observed between groups at baseline except that baseline FeNO was significantly higher in reflexology group.

### Blood eosinophil count

Mean blood eosinophil counts at baseline were similar in the three treatment groups ([Table 1](#)). Post-treatment counts at week 26 remained essentially unchanged in reflexology (0.38 (95% CI 0.27; 0.48)) and homeopathy groups (0.27 (95% CI 0.14; 0.39)). However, there was an insignificant reduction in conventional treatment group (0.28 (95% CI 0.17; 0.39)). The mean differences from baseline to week 52 were 0.03 (increased of 7%) in reflexology group, 0.01 (increased of 5%) in homeopathy group and 0.02 (increased of 6%) in conventional treatment group. After 26 and 52 weeks of therapy, there was no significant change in blood eosinophil count between the groups.

### Serum eosinophil cationic protein

At baseline, there was no significant difference between the groups in s-ECP concentrations. S-ECP decreased

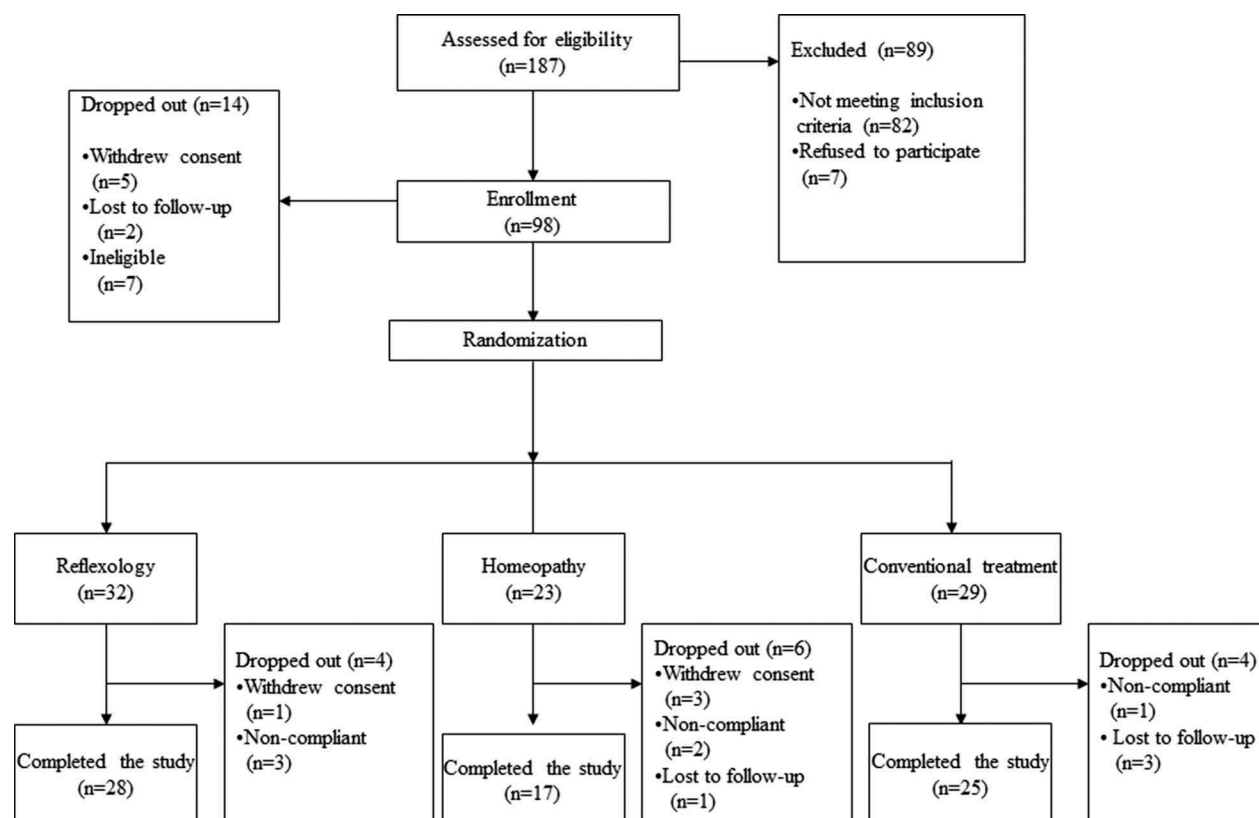
compared to baseline at week 26 in all treatment groups but no statistical significance was achieved versus baseline and between groups ([Figure 3](#)). Likewise, there was no significant difference between treatment groups at week 52.

### Exhaled nitric oxide

The FeNO level was significantly higher in the reflexology group at baseline compared to the conventional and homeopathic treatment groups ( $p = 0.01$ ). At week-52, FeNO was still significantly higher in reflexology group compared to the conventional and homeopathic treatment groups. However, the differences at week-26 and at week-52 compared to baseline were not statistically significant between groups ([Figure 3](#)).

### Methacholine challenge test

The geometric mean values for PD<sub>20</sub> at randomization were similar between groups at baseline. There were no significant changes between groups at week 26 ([Table 2](#)). At the end of study, hyperresponsiveness to methacholine improved in the three groups without statistically significant difference between the groups.



**Figure 2.** Consort diagram of the trial profile.



**Table 1.** Baseline demographic and asthma characteristics of the 84 subjects randomized in the study (ITT population) data are expressed as numbers and mean (SD) or geometric mean (CI).

	Reflexology + Conv.treatment, N = 32	Homeopathy + Conv.treatment, N = 23	Conv. treatment, N = 29	P-value
Gender				
Female/Male, n	19/13	16/7	19/10	0.81
Age (years)				
Mean, range	47.7 (20–79)	40.3 (18–67)	44.6 (19–79)	0.25
Atopy, n (%)				
(positive result in Phadiotop panel)	19.0 (59.4)	17 (73.9)	23 (79.3)	0.38
Smoking status				
Never smokers, n (%)	16 (50.0)	15 (65.2)	16 (55.2)	0.63
Ex-smokers, n (%)	14 (43.7)	7 (30.4)	11 (37.9)	
Smokers, n (%)	2 (6.3)	1 (4.4)	2 (6.9)	
FEV <sub>1</sub> /FVC(L)				
Baseline, mean ± SD	3.0 ± 0.9/3.95 ± 1.2	3.1 ± 0.8/4.0 ± 1.1	3.0 ± 0.8/3.95 ± 0.9	0.90/0.98
Total medication score				
Baseline, mean ± SD	3.47 ± 1.3	3.48 ± 1.3	3.55 ± 1.2	0.96
Blood eosinophils, 10 <sup>9</sup> /L				
Baseline, mean ± SD	0.38 ± 0.36	0.27 ± 0.17	0.29 ± 0.25	0.99
Blood ECP, µg/L				
Baseline, geometric mean (CI)	18(14; 24)	17(13; 24)	20(15; 26)	0.36
FeNO, ppb				
Baseline, geometric mean (CI)	31(23; 41)	16(11; 22)	19(14; 26)	0.01*
PD20, µg				
Baseline, geometric mean (CI)	874(470; 1625)	451(217; 936)	712(371; 1365)	0.37

\*p &lt; 0.05.

### Total medication score

Total medication scores at baseline are presented in Table 1 and no significant differences between the groups were found for the change from baseline at 26 weeks or 52 weeks.

### Adherence to study

Twenty-eight patients (88%) in reflexology, 17 in homeopathy (68%) and 25 in conventional treatment group (86%) completed the study. Withdrawal differences between groups were not statistically significant.

### Discussion

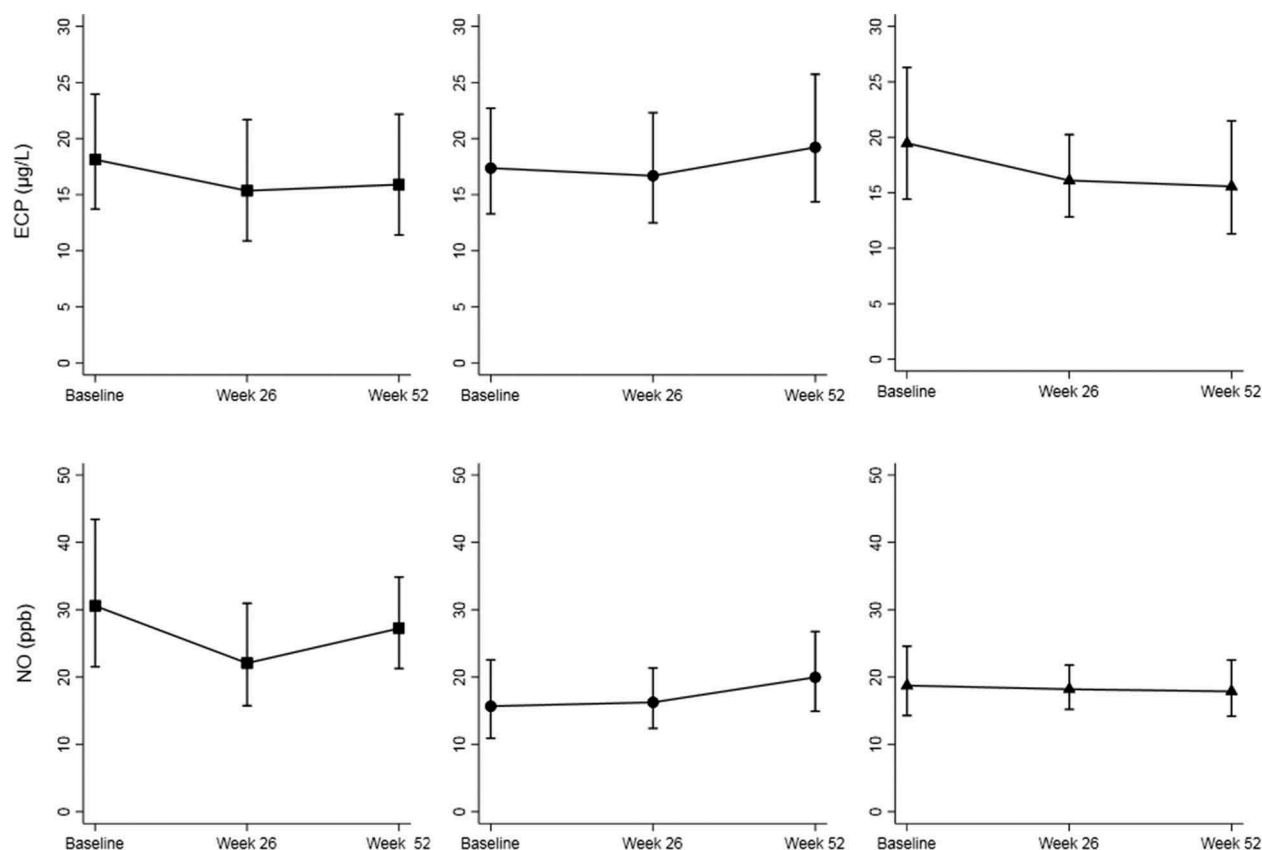
This is to our knowledge among the first studies to investigate the effect of reflexology and homeopathy added to conventional treatment in asthma on markers of airway inflammation and bronchial hyperresponsiveness. BHR and markers of inflammation were measured in a prospective, investigator-blind, randomized, controlled study design. The present study found that reflexology and homeopathy added to conventional treatment in asthma had no effect on key components of airway inflammation and BHR.

Blood eosinophils, s-ECP and F<sub>e</sub>NO are the most commonly used markers of inflammatory activity in asthma for predicting exacerbation and monitoring of

therapeutic response. This study evaluated blood eosinophils, s-ECP, F<sub>e</sub>NO and PD20 methacholine to determine whether there were any changes in markers of airway inflammation and BHR after treatment with reflexology and homeopathy.

Measurements that demonstrate the pharmacological effect of homeopathy and reflexology in asthma are limited. Two previous studies showed that treatment with homeopathy in asthma was associated with a significant reduction in blood eosinophil count and serum IgE. Matusiewicz compared the efficacy of homeopathy and placebo in 103 corticosteroid-dependent asthma patients before and after 20 weeks treatment. S-ECP and IgE levels decreased significantly in patients who were treated with homeopathy compared to placebo [14]. The same author reported similar result from a prospective, placebo-controlled and double-blind study with a complex remedy in 84 asthma patients [15]. However, both studies had inadequate allocation concealment.

The relationship between blood eosinophil count and asthma has been known for a long time. Blood eosinophils correlate with disease activity and the level of bronchial obstruction [3 20,]. However, s-ECP has been reported to be a better marker than blood eosinophil count in assessing disease activity [4 21 22,]. During our study, there were no significant changes between groups in blood eosinophil count. Likewise, no significant differences were observed between



**Figure 3.** s-ECP and  $F_{eNO}$  at baseline and after 26 and 52 weeks of study. s-ECP and  $F_{eNO}$ ; result is given as geometric mean and 95% CI.

**Table 2.** PD<sub>20</sub> at randomization and after 26 and 52 weeks treatment.

PD <sub>20</sub> (µg)	Reflexology + Conv. treatment, N = 32	Homeopathy + Conv. treatment, N = 23	Conv. Treatment, N = 29	p-Value
Randomization	874.4 [470.5; 1625.0]	450.5 [216.9; 935.9]	712.1 [371.4; 1365.5]	0.39
Week 26	750.0 [388.0; 1450.1]	488.9 [224.6; 1063.9]	1226.1 [601.3; 2402.3]	0.23
Week 52	1184.4 [529.3; 2360.2]	512.3 [227.1; 1155.5]	1052.4 [510; 2171.4]	0.26

Results are given as geometric mean and 95% CI.

groups in s-ECP levels. At baseline, 53% of patients receiving reflexology, 52% of patients receiving homeopathy and 59% of patients receiving conventional asthma treatment had serum ECP concentration above 15 µg/l, the reference value associated with significant airway inflammation in asthma.

An alternative method for evaluation of airway inflammation in asthma is the measurement of  $F_{eNO}$ .  $F_{eNO}$  is a simple and non-invasive method for identifying eosinophilic inflammation. The ATS guideline for interpretation of  $F_{eNO}$  recommends  $F_{eNO}$  measurement for monitoring both response and adherence to

anti-inflammatory treatment of eosinophilic asthma [23]. At baseline, reflexology group had a significantly higher value for  $F_{eNO}$ . The geometric mean of  $F_{eNO}$  was 30 ppb at baseline, 22 ppb at week-26 and 27 ppb at week-52. According to ATS guidelines, a reduction of more than 10 ppb for  $F_{eNO}$  values lower than 50 ppb as the cut point indicates a significant response to therapy [23]. In the present study, 10 ppb or more decrease in geometric mean  $F_{eNO}$  values was not achieved in the reflexology group. Furthermore, the measurement of  $F_{eNO}$  did not show differences between groups during follow up. This result is consistent with data from a study which evaluated a homeopathic preparation of house dust mite or cat dander (or both) for 4 weeks in 12 asthmatic children [24].

Bronchial provocation tests are useful to diagnose and assess severity of asthma [25]. BHR can be assessed using direct (methacholine, histamine) and indirect (examples such as exercise, eucapnic voluntary hyperventilation, mannitol) challenge methods [26]. Direct tests have been reported as more sensitive to detect changes in BHR [27]. In the present study, the severity of BHR at baseline in all three groups was mild and

was further reduced through the study without differences between the groups. Reflexology and homeopathic treatments were not associated with significant changes in our study. In a controlled study, Brygge et al. compared the efficacy of reflexology and placebo reflexology in 40 asthma patients before and after 10-weeks intervention, they also reported the same degree of improvement in BHR but there were no significant differences between groups [10].

Strengths of this study include prospective randomized controlled study design, objective confirmation of asthma diagnosis and detailed assessment of several inflammation markers and BHR. Due to low recruitment rates, the study timeline has doubled beyond enrolment period. The absence of significant reversibility was the most common failure in meeting recruitment, although 74 patients (88%) had a positive reversibility test, defined as increase in  $FEV_1 \geq 12\%$  and  $\geq 200$  ml after inhalation of 400  $\mu$ g salbutamol. Only four patients had positive reversibility test, defined as increase in  $FEV_1 \geq 10\%$  after inhalation of 400  $\mu$ g salbutamol but these patients had moderate to severe BHR at baseline, even though they were on anti-asthmatic treatment. However, there are some limitations to this study. One limitation is that the study population was not selected on the basis of serum ECP,  $F_eNO$  or peripheral blood eosinophil count. Although asthma has been considered to be classically a  $Th_2$  mediated chronic inflammatory diseases, there are many different phenotypes of asthma [28]. Consequently, measuring inflammation markers targeting only eosinophilic airway inflammation may not be optimal for all forms of asthma. Further limitation was that BHR was measured by direct challenge test (methacholine). Indirect challenge tests such mannitol act via inflammatory cells in the airway and positive response to mannitol indicates ongoing active airway inflammation. BHR to mannitol correlates better than Methacholine with airway inflammation and allowing better monitoring of disease activity [7]. Another limitation was that total lifetime consumption of tobacco was restricted to less than 10 pack-years but patients with a current or recent smoking history were not excluded from the study. Current smokers were only requested to avoid smoking on examination days. Inflammatory effect of smoking could have masked the exact measurements of selected markers and BHR. However, no difference was observed between groups with regard to smoking status.

The early closure of recruitment in the homeopathy group restricted the number of patients completing the study. It is possible that this could have limited the ability to detect a significant difference. However, we do not believe that this impacts the study power profoundly due to lower randomization ratio [29].

Another potential explanation for the lack of efficacy is that study patients had adequate asthma control [19]. Recruiting patients with more symptoms would have served better to investigate possible effect.

Explanation for possible mechanisms of action for both homeopathy and reflexology are important and can only be validated through scientifically based research. The present study widely investigated markers of airway inflammation and BHR. Positive results could serve as proof that homeopathy and reflexology interfere with airway inflammation and BHR. Although our results show that homeopathy and reflexology had no effect on neither of the investigated parameters, we are unable to completely rule out a possible anti-inflammatory effect in patients with more severe asthma. A larger study specifically directed at an asthma population with evidence of eosinophilic inflammation would be needed to investigate the possible effect of homeopathy and reflexology on inflammation markers and BHR.

In conclusion, this randomized trial of homeopathy or reflexology in addition to conventional asthma treatment failed to demonstrate statistically significant improvements after 1 year in any of the selected markers of airway inflammation or BHR that we evaluated. We recommend further effectiveness trials in patients with inadequately controlled asthma to take our study limitations into account. Furthermore, since asthma is a heterogeneous disease, we recommend to predefine the study population according to the type of underlying inflammation before evaluation of treatment effects.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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