



## Effect of acupuncture on house dust mite specific IgE, substance P, and symptoms in persistent allergic rhinitis

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### ABSTRACT

**Background:** Clinical evidence suggests that acupuncture improves symptoms in persistent allergic rhinitis, but the physiologic basis of these improvements is not well understood.

**Objective:** A randomized, sham-controlled trial of acupuncture for persistent allergic rhinitis in adults investigated possible modulation of mucosal immune responses.

**Methods:** A total of 151 individuals were randomized into real and sham acupuncture groups (who received twice-weekly treatments for 8 weeks) and a no acupuncture group. Various cytokines, neurotrophins, proinflammatory neuropeptides, and immunoglobulins were measured in saliva or plasma from baseline to 4-week follow-up.

**Results:** Statistically significant reduction in allergen specific IgE for house dust mite was seen only in the real acupuncture group, from 18.87 kU/L (95% CI, 10.16–27.58 kU/L) to 17.82 kU/L (95% CI, 9.81–25.83 kU/L) ( $P = .04$ ). A mean (SE) statistically significant down-regulation was also seen in proinflammatory neuropeptide substance P (SP) 18 to 24 hours after the first treatment from 408.74 (299.12) pg/mL to 90.77 (22.54) pg/mL ( $P = .04$ ). No significant changes were seen in the other neuropeptides, neurotrophins, or cytokines tested. Nasal obstruction, nasal itch, sneezing, runny nose, eye itch, and unrefreshed sleep improved significantly in the real acupuncture group (postnasal drip and sinus pain did not) and continued to improve up to 4-week follow-up.

**Conclusion:** Acupuncture modulated mucosal immune response in the upper airway in adults with persistent allergic rhinitis. This modulation appears to be associated with down-regulation of allergen specific IgE for house dust mite, which this study is the first to report. Improvements in nasal itch, eye itch, and sneezing after acupuncture are suggestive of down-regulation of transient receptor potential vanilloid 1.

**Trial Registration:** Australian New Zealand Clinical Trials Registry Identifier: ACTRN 12610001052022.

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### Introduction

The pathogenesis of allergic rhinitis involves a complex cross-talk among cytokines, neurotrophins, and proinflammatory neuropeptides.<sup>1</sup> Acupuncture has been found to improve symptoms and quality of life in patients with allergic rhinitis, and there is

evidence that acupuncture may modulate some biomarkers.<sup>2</sup> Although down-regulation of substance P (SP), vasoactive intestinal peptide (VIP), and total IgE after acupuncture has been previously reported, no studies to date have investigated potential modulation of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF).<sup>2,3</sup> We hypothesize that acupuncture may down-regulate neurotrophins, proinflammatory neuropeptides, and IgE and shift  $T_H1/T_H2$  balance away from  $T_H2$  dominance, while simultaneously reducing nasal mucosal inflammation and hypersensitivity.<sup>4</sup> To test this hypothesis, a randomized, sham-controlled trial of acupuncture treatment for persistent allergic rhinitis was undertaken in which cytokines, neurotrophins, proinflammatory neuropeptides, IgE, nasal airway clearance, symptoms, and quality of life were measured.

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**Group Information:** The members of the Mucosal Immunology Research Group are Nicholas West, PhD, Ibtisam Ghazawi, PhD, Pauline Low, PhD, and Ann-Christen Bischoff.

## Methods

### Trial Design, Ethics Approval, and Trial Registration

The study was a 3-arm, participant- and assessor-masked, parallel, randomized, sham-controlled trial. Initial screening, recruitment, and follow-up phases were conducted at a private allergy clinic at Southport, Queensland, in weeks 0, 9, and 12 (Fig 1). Acupuncture treatment was administered at a private acupuncture clinic also in Southport, twice weekly for 8 weeks (weeks 1 to 8). Ethical clearance for the study was obtained from the Griffith University Human Research Ethics Committee. The study was registered with the Australian New Zealand Clinical Trials Registry (Australian New Zealand Clinical Trials Registry Identifier: ACTRN 12610001052022).

### Inclusion and Exclusion Criteria

The inclusion criteria for the study were as follows: men and women aged 18 to 45 years, a more than 2-year history of moderate to severe allergic rhinitis, positive skin prick test result to 3 clinically relevant local grass pollens (Bahia grass, Johnson grass, and Bermuda grass) and/or house dust mite (*Dermatophagoides pteronyssinus*), and positive radioallergosorbent test result to house dust mite or Bermuda grass. The exclusion criteria for the study were as follows: non-allergic rhinitis, negative skin prick test result to 3 local grass pollens and/or house dust mite and negative blood test result to house dust mite or Bermuda grass, acupuncture treatment for allergic rhinitis or specific immunotherapy in the previous 2 years, respiratory diseases (eg, asthma, nasal polyposis, and chronic obstructive pulmonary disease), infectious diseases, medications that affect salivary flow and components (eg, systemic corticosteroids, diuretics, and some antidepressants), pregnancy, and nasal recreational drugs.

### Recruitment and Randomization Procedures

Participants were recruited through public media and e-mails to Griffith University students and staff. A total of 152 participants were screened (Fig 2). Participants were randomized to 1 of the 3

study groups: real acupuncture, sham acupuncture, or no acupuncture. The randomization schedule was generated using the Research Randomizer tool (<http://www.randomizer.org>), and on enrollment, each participant was allocated to the next available line on the schedule. Recruitment was conducted in Southport, Queensland, between October 2009 and May 2012, and the trial was completed in August 2012.

### Masking

Participants in the real acupuncture and sham acupuncture groups were masked to group allocation, and this masking was later confirmed to have been successful by the exit debrief questionnaire results. Staff at the allergy clinic who performed clinical assessments and laboratory staff who performed tests on saliva and blood were masked to group allocations. Data entry and statistical analysis were also performed with masking of group allocations.

### Sample Size Calculation

A power analysis was performed using Sample Power (IBM SPSS, Dublin, Ireland). A sample size of 36 for each group was predicted to provide 80% power with a type 1 error rate of 5% (2-tailed).

### Outcome Measures

The primary outcome for the study was any modulation in mucosal immune response in the upper respiratory tract after acupuncture treatment. Measurements included total and allergen specific IgE, proinflammatory neuropeptides, neurotrophins, and cytokines. The secondary outcome was to measure changes in symptoms, quality of life, and nasal airway clearance.

### Saliva Collection

Samples of mixed saliva were collected using cotton cellulose eye-spears as previously described.<sup>5</sup> After collection, the samples were placed immediately in a  $-18^{\circ}\text{C}$  freezer and transported to the laboratory, where the samples were frozen in liquid nitrogen and stored at  $-70^{\circ}\text{C}$  until further processed. When the sample was

| Week 0                                                                                             | Week 1                            | Week 2 | Week 3                  | Weeks 4 and 5 | Week 6                  | Weeks 7 and 8 | Week 9                      | Weeks 10 and 11 | Week 12                                                                                            |
|----------------------------------------------------------------------------------------------------|-----------------------------------|--------|-------------------------|---------------|-------------------------|---------------|-----------------------------|-----------------|----------------------------------------------------------------------------------------------------|
| Allergy clinic                                                                                     | Acupuncture clinic                |        |                         |               |                         |               | Allergy clinic              |                 | Allergy clinic                                                                                     |
| Screening, recruitment, randomization                                                              | 2 Acupuncture treatments per week |        |                         |               |                         |               |                             |                 |                                                                                                    |
| SPT, PNIF, MITO, iTNSS, Mini-RQLQ                                                                  |                                   |        |                         |               |                         |               | PNIF, MITO, iTNSS, MiniRQLQ |                 | PNIF, MITO, iTNSS, MiniRQLQ                                                                        |
| Saliva samples: SP, VIP, ECP                                                                       | Saliva samples: SP, VIP           |        | Saliva samples: SP, VIP |               | Saliva samples: SP, VIP | Exit debrief  | Saliva samples: SP, VIP     |                 | Saliva samples: SP, VIP, ECP                                                                       |
| Daily symptom and medication diary                                                                 |                                   |        |                         |               |                         |               |                             |                 |                                                                                                    |
| QML                                                                                                |                                   |        |                         |               |                         |               |                             |                 | QML                                                                                                |
| Blood samples: RAST, IgE, CGRP, NGF, BDNF, IL-2, IL-4, IL-10, IL-12 (p70), IFN- $\gamma$ , eotaxin |                                   |        |                         |               |                         |               |                             |                 | Blood samples: RAST, IgE, CGRP, NGF, BDNF, IL-2, IL-4, IL-10, IL-12 (p70), IFN- $\gamma$ , eotaxin |

**Figure 1.** Trial design. BDNF indicates brain-derived neurotrophic factor; CGRP, calcitonin gene-related peptide; ECP, eosinophilic cationic protein; IL, interleukin; IFN- $\gamma$ , interferon  $\gamma$ ; iTNSS, instantaneous total nasal symptom score; Mini-RQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; MITO, mean inferior turbinate obstruction; NGF, nerve growth factor; PNIF, peak nasal inspiratory flow; QML, Queensland Medical Laboratories; RAST, radioallergoabsorbent test; SP, substance P; SPT, skin prick test; VIP, vasoactive intestinal peptide.

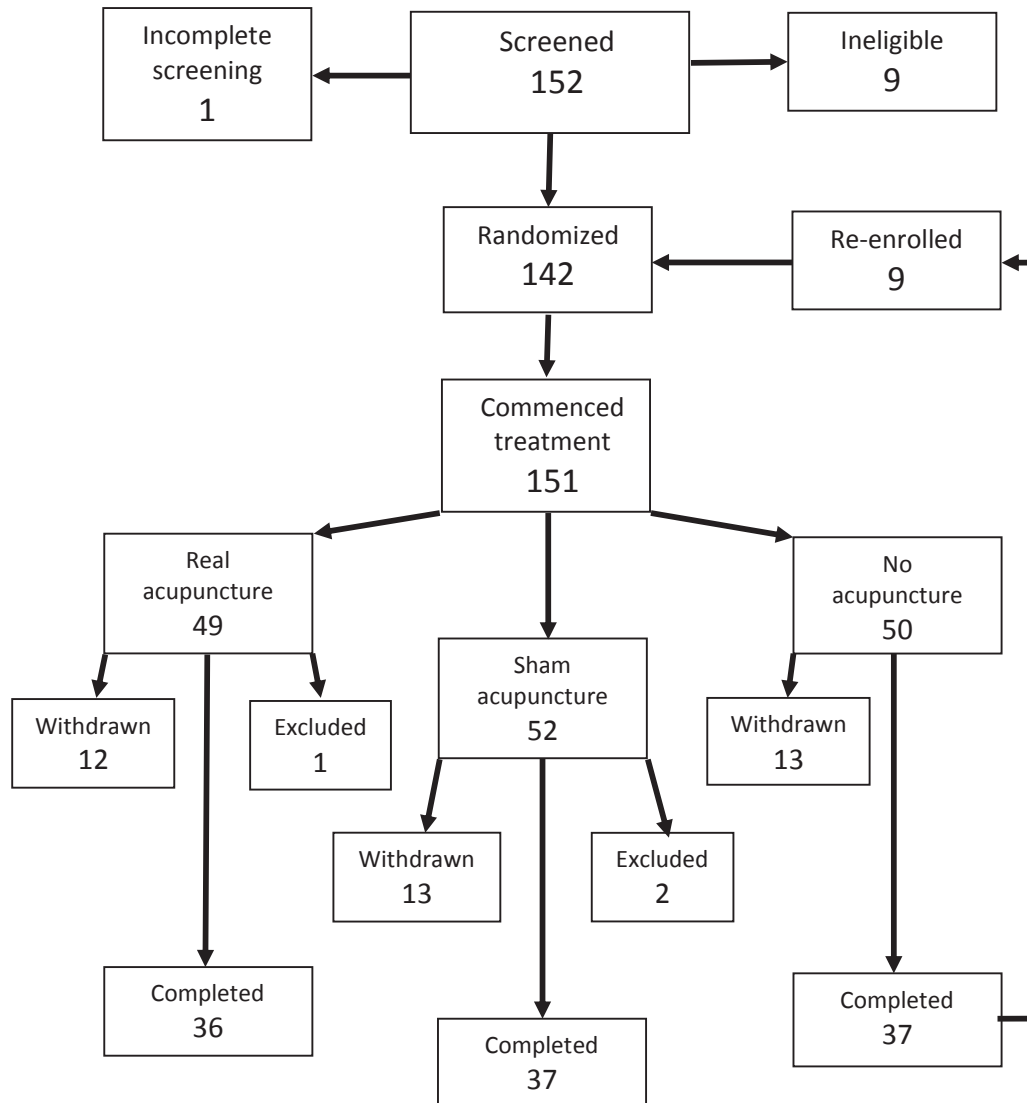


**Figure 2.** Participant flowchart.

thawed, it was centrifuged at 4°C at 1,000g to recover the saliva and used for analysis or refrozen in 0.5-mL aliquots for further analysis.

#### Blood Collection

Blood collection was performed by the commercial pathology company Queensland Medical Laboratories (Queensland, Australia). A 12.5-mL blood sample was collected by venupuncture into a plain and heparinized tube. Serum and plasma samples were frozen at –70°C in 0.5-mL aliquots until required for analysis.

#### Laboratory Analysis

Laboratory analysis (apart from immunoglobulin testing) was performed by Griffith University laboratory staff who were masked to participants' group allocations. All assays were performed with neat saliva or plasma/serum except for the BDNF plasma assay, which used a 1:20 dilution.

#### Total and Specific Antibodies

Total IgE and allergen specific IgE antibodies to house dust mite, Bermuda grass, Johnson grass (*Sorghum halepense*), and Bahia grass (*Paspalum notatum*) were measured in serum by ImmunoCAP

(Phadia, Uppsala, Sweden). All immunoglobulin testing was performed by Queensland Medical Laboratories. Enzyme-linked immunosorbent assays were conducted following the manufacturer's instructions on cytokines, neuropeptides, neurotrophins, and eosinophilic cationic protein (ECP).

#### Cytokines

Cytokines indicative of a  $T_H1$  response (interferon  $\gamma$  [IFN- $\gamma$ ], interleukin [IL] 12), a  $T_H2$  response (IL-4), and proinflammatory cytokines (IL-2 and eotaxin) and IL-10 in plasma were assayed with a EMD Millipore Human Cytokine/Chemokine Magnetic Bead Panel HCYTOMAG-60K-06 (EMD Millipore, Billerica, Massachusetts).

#### Neuropeptides and Neurotrophins

Neurotrophins and neuropeptides were assayed with the following commercial kits: HNP-35K-01 (EMD Millipore) for SP, E90380Hu (USCN Life Science Inc, Wuhan, Hubei, People's Republic of China) for VIP, E90876Hu (USCN Life Science Inc) for calcitonin gene-related peptide (CGRP), human adipokine kit HADK2-61K-BO1 (EMD Millipore) for NGF, and Chemikine BDNF Sandwich enzyme-linked immunosorbent assay CYT306 (EMD Millipore) for BDNF.

### Eosinophilic Cationic Protein

ECP was assayed in saliva using Mesacup 7618E supplied by Medical and Biological Laboratories International (Woburn, Massachusetts).

### Instantaneous Total Nasal Symptom Score

Participants were scored on a scale from 0 (not at all) to 3 (severe) on 4 symptoms at the allergy clinic at week 0 (on recruitment), week 9 (1-week follow-up after treatment), and week 12 (4-week follow-up after treatment). The 4 symptoms were runny nose, itchy nose, stuffy nose, and sneezing.

### Mini-Rhinoconjunctivitis Quality of Life Questionnaire

Participants completed the Mini-Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) at the allergy clinic in weeks 0, 9, and 12. The Mini-RQLQ contains 14 items scored on a scale of severity from 0 (not affected) to 6 (extremely affected): regular activities, recreational activities, sleep, need to rub nose or eyes, need to blow nose repeatedly, sneezing, stuffy or blocked nose, runny nose, itchy eyes, sore eyes, watery eyes, tiredness and/or fatigue, thirst, and feeling irritable. The 14 items were divided into 5 domains: activity score, practical problems score, nasal symptoms score, eye symptoms score, and other symptoms score.

### Daily Symptom and Medication Diary

Participants completed a daily symptom and medication diary from week 1 to week 12. The presence or absence of 7 symptoms was recorded daily: nasal itch, eye itch, sneezing, runny nose, postnasal drip, unrefreshed sleep, and sinus pain. Weekly symptom scores were calculated from a total of 49 (7 symptoms for 7 days). All medications taken during the trial were also recorded daily, yielding a weekly score of a total of 7.

### Mean Inferior Turbinate Obstruction

Mean (between left and right) inferior turbinate obstruction (MITO) scores (expressed as a percentage of the nasal airway space) were measured with visual inspection by the allergologist in weeks 0, 9, and 12.

### Peak Nasal Inspiratory Flow

Peak nasal inspiratory flow (PNIF) was measured by the clinical assistant at the allergy clinic using anterior active rhinomanometry according to the International Committee for the Standardization of Rhinomanometry guidelines.<sup>6,7</sup> The PNIF was measured at weeks 0, 9, and 12.

### Real Acupuncture Treatment

#### Acupuncture point selection

The rationale for acupuncture point selection in this study was based on 3 sources of data: points frequently used in research studies, points frequently recommended in modern acupuncture textbooks in the clinical sections, and finally points for which indications relevant to allergic rhinitis frequently appear in the point indications sections of modern texts.<sup>8–23</sup> The following points were chosen for this study: Yintang, LI 20, LI 4, ST 36, and GV 23. All points were located according to the World Health Organization International Standard Acupuncture Point Locations in the Western Pacific Region.<sup>24</sup>

#### Duration and Frequency of Acupuncture Treatment

A review of previous studies on acupuncture for allergic rhinitis indicated that a treatment regimen of twice-weekly treatments for 6 to 8 weeks produced significantly superior clinical outcomes

when compared with studies that used shorter or less frequent treatments.<sup>8–14,25–27</sup> Therefore, treatments were given twice weekly for 8 weeks, with a 2- to 4-day break between treatments.

### Needle Technique

Traditional Chinese-style single-use disposable stainless steel needles (0.25 × 40 mm) (C and G acupuncture needles; Helio Supply Co Pty Ltd, Sydney, Australia) were used. The needles were inserted at the indicated points but not manipulated. Yintang, LI 20, and GV 23 were needled obliquely to a depth of 3 to 5 mm, whereas LI 4 and ST 36 were needled perpendicularly to a depth of 10 to 15 mm. Needles were retained for 20 minutes (without manipulation) and then removed.

### Time of Treatment

To reduce the influence of circadian variations, all acupuncture treatments were performed between 6 AM and midday, twice weekly.

### Sham Acupuncture Treatment

Non-channel points used in sham acupuncture protocols have been shown not to be inert<sup>28,29</sup>; however, because there is no sham acupuncture protocol that has been validated as inert,<sup>30,31</sup> needling non-channel points was the most appropriate invasive sham protocol available.

### Acupuncture point selection

For the sham acupuncture group, 4 sites (needled bilaterally) were selected, which did not correspond to the locations of known acupuncture points and did not lie on identified acupuncture channels (meridians). Midline points on the head were avoided because this would lie on an identified acupuncture channel, the governor vessel (Dumai). The acupuncture points were as follows: forehead sham point: 1 cun lateral to GB 14 (Yangbai); cheek sham point: the midpoint of the line between LI 20 and SI 19 (Tinggong); hand sham point: on the dorsum of the hand, at the midpoint of the second metacarpal bone on the ulnar side of the bone; and leg sham point: on the lateral aspect of the lower leg, 1 cun below the point Linghou (M-LE-24). The forehead sham point was needled obliquely, whereas the cheek sham was needled perpendicularly, both to a depth of 2 to 3 mm. Hand and leg sham points were needled perpendicularly to a depth of 5 to 10 mm and 10 to 15 mm, respectively.

### Other treatment parameters

The frequency and duration of sham acupuncture treatment were the same as the real acupuncture group, as was the needle technique and timing of treatment. All acupuncture treatments were given by an acupuncturist (J.L.M.) who has bachelor of health science (acupuncture) and master of acupuncture degrees and more than 35 years of clinical experience as an acupuncturist, including decades of experience in treating allergic rhinitis.

### Cointerventions

All participants were permitted to use nonsteroidal oral relief medications throughout the trial, which they recorded in a daily symptom and medication diary.

### Statistical Analysis

All values from laboratory analysis were standardized across plates (using mean ratios of all available duplicate tests) before statistical analysis. All data were tested for normality with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Nonnormal data were log transformed and then retested for normality. To compare time points within groups, paired-sample *t* tests were used

whenever data (natural or logged) were normal or the Friedman test for data which were not normally distributed. Between-group analyses were conducted using independent-sample *t* tests for normally distributed data and independent-sample Kruskal-Wallis tests for nonparametric data. Correlation analyses were conducted using the Spearman  $\rho$ . Statistical calculations were conducted using SPSS statistical software for Windows, version 21 (SPSS Inc, Chicago, Illinois). Missing values and outliers for biomarkers (values lying outside the published upper and lower detection limits for each biomarker) were excluded from all analyses. Missing values in measures for symptoms, quality of life, and nasal airway clearance for the 110 participants who completed the study were imputed using last datum carried forward. Valid multivariate analysis of variance tests could not be performed because normality tests and multivariate tests failed for most of the data.

## Results

### Baseline Characteristics

There were no statistically significant differences between groups at baseline in sex, age, total IgE, allergen specific IgE, NGF, BDNF, SP, VIP, CGRP, ECP, eotaxin, symptom severity, PNIF or MITO. However, there were some significant between-group differences in IL-2, IL-4, IL-10, IL-12 (p70), and IFN- $\gamma$ , with the no acupuncture group having significantly higher levels of these cytokines than the sham acupuncture group. Because these cytokines had no significant changes after treatment, these baseline differences are unlikely to have had any effect on the results of the study.

### Primary Outcomes

#### Total and specific antibodies

There were significant mean (95% CI) decreases in total serum IgE between week 0 and week 12 from 217.56 (60.27, 374.86) kU/L to 191.91 (53.58, 330.23) kU/L ( $P = .02$ ) in the real acupuncture group and from 299.31 (165.40, 433.23) to 269.46 (153.32, 385.60) kU/L ( $P = .02$ ) in the sham acupuncture group but no significant difference in the no acupuncture group (Table 1). There were no significant differences between groups at week 0 or week 12.

A statistically significant mean (95% CI) reduction was found in serum allergen specific IgE for house dust mite at week 12 (compared with week 0) after real acupuncture from 18.87 (10.16, 27.58) kU/L to 17.82 (9.81, 25.83) kU/L ( $P = .04$ ). No significant differences were seen after sham acupuncture or no acupuncture (Table 1). No differences were seen between week 0 and week 12 in 3 regional grass pollens (Bahia grass, Johnson grass, and Bermuda grass) for any of the groups with only one exception. In the no acupuncture group, there was an unexplained statistically significant reduction in allergen specific IgE for Bahia grass between week 0 and week 12 ( $P = .01$ ).

**Table 1**

Total IgE and Allergen Specific IgE for House Dust Mite In Serum: Time Point Comparisons Within Groups

| Group                     | Mean (95% CI)                        |                                  |
|---------------------------|--------------------------------------|----------------------------------|
|                           | Total IgE, kU/L                      | House dust mite IgE, kU/L        |
| No acupuncture (n = 34)   |                                      |                                  |
| Week 0                    | 337.71 (145.95, 529.46)              | 29.98 (18.14, 41.81)             |
| Week 12                   | 306.15 (139.02, 473.27)              | 29.61 (17.83, 41.39)             |
| Sham acupuncture (n = 35) |                                      |                                  |
| Week 0                    | 299.31 (165.40, 433.23)              | 31.22 (20.00, 42.44)             |
| Week 12                   | 269.46 (153.32, 385.60) <sup>a</sup> | 29.94 (19.36, 40.53)             |
| Real acupuncture (n = 32) |                                      |                                  |
| Week 0                    | 217.56 (60.27, 374.86)               | 18.87 (10.16, 27.58)             |
| Week 12                   | 191.91 (53.58, 330.23) <sup>a</sup>  | 17.82 (9.81, 25.83) <sup>a</sup> |

<sup>a</sup> $P < .05$  compared with week 0.

### Cytokines

Cytokines indicative of a  $T_H1$  response (IFN- $\gamma$ , IL-12), a  $T_H2$  response (IL-4), and proinflammatory cytokines (IL-2 and eotaxin) and IL-10 were measured, but there were no significant differences in any cytokine between week 0 and week 12 in any group.

### Neuropeptides and Neurotrophins

In the real acupuncture group, there were significant decreases in salivary SP between week 1 before treatment and 18 to 24 hours after treatment in both week 1 ( $P = .04$ ) and week 3 ( $P = .04$ ) (Table 2). In the sham acupuncture group, there were significant decreases in SP between week 1 before treatment and week 6 (18 to 24 hours after treatment) ( $P = .03$ ). There were no significant differences between time points in the no acupuncture group. There were significant differences between the real acupuncture and no acupuncture groups at week 3 ( $P = .002$ ) and week 6 ( $P = .02$ ) and between sham acupuncture and no acupuncture at week 3 ( $P = .03$ ) and week 6 ( $P = .003$ ). There were no significant differences between groups at week 12 and no significant differences between the real and sham acupuncture groups at any time point.

Salivary VIP levels were significantly lower in the real acupuncture group compared with the sham acupuncture group at week 1 (18–24 hours after treatment) ( $P = .04$ ); however, there were no significant differences between time points in any group.

There were no significant differences in CGRP, NGF, or BDNF between week 0 and week 12 in any group. This is the first study, to our knowledge, to examine NGF and BDNF after acupuncture for allergic rhinitis.

### Secondary Outcomes

#### Instantaneous total nasal symptom score

Within the real acupuncture group, there was a significant reduction in instantaneous total nasal symptom score (iTNSS) between week 0 and week 9 (28.2%;  $P = .01$ ) and between week 0 and week 12 (34.3%;  $P = .003$ ) (Table 3). No significant differences were seen between time points within the sham and no acupuncture

**Table 2**

Substance P in Saliva: Time Point Comparisons Within Groups

| Group                         | Mean (SE), pg/mL | Logged mean (SE), pg/mL | Logged mean (SE) difference from week 1 before treatment | P value (2-tailed) |
|-------------------------------|------------------|-------------------------|----------------------------------------------------------|--------------------|
| No acupuncture                |                  |                         |                                                          |                    |
| Week 1 (n = 37)               | 428.26 (112.13)  | 2.05 (0.15)             |                                                          |                    |
| Week 3 (n = 37)               | 383.24 (94.21)   | 2.02 (0.14)             | 0.03 (0.08)                                              | .69                |
| Week 6 (n = 37)               | 464.31 (144.79)  | 2.02 (0.14)             | 0.03 (0.67)                                              | .49                |
| Week 12 (n = 37)              | 491.03 (252.04)  | 1.95 (0.15)             | 0.06 (0.54)                                              | .42                |
| Sham acupuncture              |                  |                         |                                                          |                    |
| Week 1 pre (n = 36)           | 413.37 (299.50)  | 1.69 (0.14)             |                                                          |                    |
| Week 1 (18–24 hours) (n = 36) | 536.80 (337.65)  | 1.40 (0.16)             | 0.29 (0.17)                                              | .10                |
| Week 3 (18–24 hours) (n = 33) | 603.60 (362.52)  | 1.53 (0.18)             | 0.10 (0.16)                                              | .52                |
| Week 6 (18–24 hours) (n = 34) | 401.16 (317.78)  | 1.41 (0.16)             | 0.33 (0.14)                                              | .03 <sup>a</sup>   |
| Week 12 (n = 36)              | 742.14 (416.16)  | 1.76 (0.17)             | −0.07 (0.16)                                             | .68                |
| Real acupuncture              |                  |                         |                                                          |                    |
| Week 1 pre (n = 36)           | 408.74 (299.12)  | 1.75 (0.14)             |                                                          |                    |
| Week 1 (18–24 hours) (n = 34) | 90.77 (22.54)    | 1.57 (0.12)             | 0.24 (0.11)                                              | .04 <sup>a</sup>   |
| Week 3 (18–24 hours) (n = 33) | 74.19 (16.84)    | 1.40 (0.14)             | 0.34 (0.16)                                              | .04 <sup>a</sup>   |
| Week 6 (18–24 hours) (n = 33) | 110.42 (29.94)   | 1.57 (0.13)             | 0.20 (0.18)                                              | .26                |
| Week 12 (n = 36)              | 240.72 (114.86)  | 1.64 (0.14)             | 0.11 (0.16)                                              | .48                |

<sup>a</sup> $P < .05$  compared with week 1 before treatment.

**Table 3**  
Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) Total Scores

| Week | No acupuncture<br>(n = 37) |       | Sham acupuncture<br>(n = 37) |       | Real acupuncture<br>(n = 36) |       |
|------|----------------------------|-------|------------------------------|-------|------------------------------|-------|
|      | Mean (SE)                  | SD    | Mean (SE)                    | SD    | Mean (SE)                    | SD    |
| 0    | 43.62 (2.58)               | 15.69 | 46.89 (2.11)                 | 12.86 | 44.33 (2.72)                 | 16.31 |
| 9    | 44.43 (1.95)               | 11.88 | 34.51 (3.01) <sup>a</sup>    | 18.32 | 34.06 (3.12) <sup>a</sup>    | 18.72 |
| 12   | 40.78 (2.72)               | 16.52 | 38.73 (3.17) <sup>b</sup>    | 19.25 | 30.72 (2.93) <sup>a</sup>    | 17.59 |

<sup>a</sup>P < .001 compared with week 0.

<sup>b</sup>P < .05 compared with week 0.

groups. There were no significant between-group differences at any time point.

#### Mini-Rhinoconjunctivitis Quality of Life Questionnaire

There were significant reductions in total Mini-RQLQ scores between week 0 and week 9 in the real acupuncture group (23.2%;  $P = .001$ ) and the sham acupuncture group (26.4%;  $P = .001$ ). There were also significant reductions between week 0 and week 12 in the real acupuncture group (30.7%;  $P = .001$ ) and the sham acupuncture group (17.4%;  $P = .007$ ) (Table 3). There were significant differences between the no acupuncture group and both the real acupuncture ( $P = .006$ ) and the sham acupuncture ( $P = .007$ ) groups at week 9 and between the no acupuncture and real acupuncture groups at week 12 ( $P = .01$ ). Although there is no significant difference between the real and sham acupuncture groups in Mini-RQLQ scores at week 9, there is a consistent pattern in total scores and across all 5 domains, which reveals continued improvement in the real acupuncture group between week 9 and week 12 but deterioration in the sham acupuncture group.

#### Daily symptom and medication diary

Of the 110 participants who completed the study, 88 submitted their daily symptom and medication diaries. In the real acupuncture group, there were significant differences between total weekly symptom scores for week 1 and week 3 ( $P = .02$ ), and these differences persisted every week until week 12 (Table 4). The percentage improvement in daily symptom diary scores from week 1 to week 12 was 24.4%. There were no significant differences between week 1 and any other week in the other groups. When the 7 symptoms included in the daily symptom diary were examined separately, 5 symptoms improved significantly in the real acupuncture group (nasal itch, eye itch, sneezing, runny nose, and unrefreshed sleep), whereas 2 symptoms did not improve (post-nasal drip and sinus pain) (Table 5). In the sham acupuncture group, the only symptom that improved significantly was unrefreshed sleep. There were no changes in the no acupuncture group. After real acupuncture, the percentage improvement from week 1 to

**Table 4**  
Daily Symptom Diary Mean Weekly Total Scores

| Week | No acupuncture (n = 27) |       | Sham acupuncture (n = 31) |       | Real acupuncture (n = 30) |       | P value           |
|------|-------------------------|-------|---------------------------|-------|---------------------------|-------|-------------------|
|      | Mean (SE)               | SD    | Mean (SE)                 | SD    | Mean (SE)                 | SD    |                   |
| 1    | 19.19 (2.39)            | 12.40 | 19.03 (1.91)              | 10.65 | 23.27 (2.68)              | 14.67 | ...               |
| 2    | 19.00 (2.72)            | 14.12 | 19.52 (1.89)              | 10.53 | 21.73 (2.89)              | 15.81 | ...               |
| 3    | 18.63 (2.74)            | 14.24 | 18.81 (1.89)              | 10.53 | 20.33 (2.98)              | 16.34 | .02 <sup>a</sup>  |
| 4    | 18.85 (2.59)            | 13.47 | 16.61 (2.22)              | 12.37 | 18.97 (3.14)              | 17.20 | .007 <sup>a</sup> |
| 5    | 19.70 (2.78)            | 14.44 | 16.23 (2.27)              | 12.65 | 18.13 (3.20)              | 17.54 | .001 <sup>b</sup> |
| 6    | 18.67 (2.64)            | 13.72 | 14.61 (2.23)              | 12.41 | 17.63 (3.13)              | 17.15 | .001 <sup>b</sup> |
| 7    | 19.11 (2.62)            | 13.60 | 17.03 (2.15)              | 11.97 | 18.70 (3.13)              | 17.15 | .003 <sup>a</sup> |
| 8    | 17.44 (2.68)            | 13.90 | 15.42 (1.75)              | 9.73  | 18.07 (3.14)              | 17.20 | .001 <sup>b</sup> |
| 9    | 17.44 (2.78)            | 14.34 | 15.32 (2.01)              | 11.20 | 18.63 (3.22)              | 17.64 | .009 <sup>a</sup> |
| 10   | 18.37 (2.64)            | 13.70 | 15.45 (2.02)              | 11.29 | 18.50 (3.21)              | 17.60 | .01 <sup>a</sup>  |
| 11   | 19.11 (2.89)            | 15.00 | 15.42 (2.21)              | 12.33 | 18.10 (3.24)              | 17.76 | .004 <sup>a</sup> |
| 12   | 18.96 (3.05)            | 15.83 | 15.29 (2.09)              | 11.66 | 17.60 (3.37)              | 18.46 | .003 <sup>a</sup> |

<sup>a</sup>P < .05 compared with week 1.

<sup>b</sup>P < .001 compared with week 1.

week 12 and the maximal improvement in any week compared with week 1, respectively, were 47.5% and 47.5% for unrefreshed sleep, 23.3% and 35.0% for nasal itch, 20.6% and 33.0% for sneezing, 16.7% and 28.6% for runny nose, and 16.1% and 27.3% for eye itch.

#### Mean inferior turbinate obstruction

There were no significant differences within any group between time points. The only significant between-group difference was between the no acupuncture and sham acupuncture groups at week 9 ( $P = .02$ ).

#### Peak nasal inspiratory flow

There were no significant differences between groups at any time point. There were no significant differences in any group between week 0 and week 9 or between week 0 and week 12, except for a significant difference between week 0 and week 12 in the no acupuncture group ( $P = .02$ ).

#### Safety

There were no serious adverse events reported or observed during the study. There were 40 minor adverse events during the study: slight bruising ( $n = 27$ ), acute transitory pain on needle insertion ( $n = 8$ ), acute transitory pain and pins and needles sensation on insertion ( $n = 1$ ), soreness ( $n = 1$ ), soreness and itching ( $n = 1$ ), swelling ( $n = 1$ ), and tingling ( $n = 1$ ). Because approximately 1,300 acupuncture treatments were administered during the study, this represents a minor adverse events rate of approximately 3%.

#### Discussion

Four weeks after 16 sessions of real acupuncture treatment twice weekly, total IgE decreased significantly ( $P = .02$ ), whereas allergen specific IgE for house dust mite also decreased significantly ( $P = .04$ ). One previous study on acupuncture for persistent allergic rhinitis reported a posttreatment significant decrease in total IgE ( $P < .01$ ).<sup>27</sup> This was the first study to report a significant decrease in allergen specific IgE for house dust mite in adults with persistent allergic rhinitis. These findings suggest that acupuncture modulates the allergic immune response through down-regulation of allergen specific IgE for house dust mite possibly through the reduction of Th2 dominance.<sup>32</sup>

#### What About VIP?

Down-regulation of proinflammatory neuropeptide SP in saliva after acupuncture for persistent allergic rhinitis has been previously reported.<sup>3</sup> However, the course of the down-regulation of SP in this study was of particular interest because it did not correlate to the course of symptomatic improvements (Fig 3). The first time

**Table 5**  
Daily Symptom Diary Weekly Means for the Real Acupuncture Group (n = 30)

| Week | Nasal itch  |                                  |                    | Eye itch    |                                  |                   | Sneezing    |                                  |                   | Runny nose  |                                  |                  | Unrefreshed sleep |                                  |                   |
|------|-------------|----------------------------------|--------------------|-------------|----------------------------------|-------------------|-------------|----------------------------------|-------------------|-------------|----------------------------------|------------------|-------------------|----------------------------------|-------------------|
|      | Mean (SE)   | Mean (SE) difference from week 1 | P value            | Mean (SE)   | Mean (SE) difference from week 1 | P value           | Mean (SE)   | Mean (SE) difference from week 1 | P value           | Mean (SE)   | Mean (SE) difference from week 1 | P value          | Mean (SE)         | Mean (SE) difference from week 1 | P value           |
| 1    | 4.00 (0.47) |                                  |                    | 3.30 (0.53) |                                  |                   | 4.03 (0.49) |                                  |                   | 3.60 (0.55) |                                  |                  | 3.73 (0.54)       |                                  |                   |
| 2    | 3.70 (0.55) | 0.30 (0.24)                      | .21                | 2.77 (0.54) | 0.53 (0.22)                      | .02 <sup>a</sup>  | 3.73 (0.50) | 0.30 (0.35)                      | .39               | 3.57 (0.54) | 0.03 (0.36)                      | .93              | 3.53 (0.54)       | 0.20 (0.22)                      | .36               |
| 3    | 3.57 (0.57) | 0.43 (0.38)                      | .27                | 3.20 (0.53) | 0.10 (0.30)                      | .75               | 2.93 (0.50) | 1.10 (0.43)                      | .02 <sup>a</sup>  | 3.23 (0.51) | 0.37 (0.36)                      | .32              | 3.13 (0.56)       | 0.60 (0.36)                      | .11               |
| 4    | 3.57 (0.58) | 0.43 (0.41)                      | .30                | 2.97 (0.56) | 0.33 (0.38)                      | .39               | 3.00 (0.53) | 1.03 (0.34)                      | .005 <sup>a</sup> | 2.90 (0.52) | 0.70 (0.43)                      | .11              | 2.50 (0.55)       | 1.23 (0.38)                      | .003 <sup>a</sup> |
| 5    | 3.37 (0.55) | 0.63 (0.39)                      | .12                | 2.90 (0.57) | 0.40 (0.36)                      | .28               | 2.70 (0.51) | 1.33 (0.38)                      | .002 <sup>a</sup> | 2.57 (0.53) | 1.03 (0.40)                      | .01 <sup>a</sup> | 2.43 (0.57)       | 1.30 (0.42)                      | .004 <sup>a</sup> |
| 6    | 2.60 (0.52) | 1.40 (0.33)                      | <.001 <sup>b</sup> | 2.53 (0.53) | 0.77 (0.26)                      | .006 <sup>a</sup> | 3.03 (0.48) | 1.00 (0.38)                      | .01 <sup>a</sup>  | 2.90 (0.52) | 0.70 (0.47)                      | .15              | 2.53 (0.56)       | 1.20 (0.44)                      | .01 <sup>a</sup>  |
| 7    | 3.40 (0.54) | 0.60 (0.36)                      | .11                | 2.40 (0.52) | 0.90 (0.32)                      | .008 <sup>a</sup> | 3.43 (0.50) | 0.60 (0.41)                      | .15               | 2.87 (0.56) | 0.73 (0.44)                      | .11              | 2.57 (0.53)       | 1.17 (0.47)                      | .02 <sup>a</sup>  |
| 8    | 3.07 (0.53) | 0.93 (0.32)                      | .006 <sup>a</sup>  | 2.47 (0.57) | 0.83 (0.27)                      | .006 <sup>a</sup> | 3.33 (0.49) | 0.70 (0.37)                      | .07               | 3.00 (0.56) | 0.60 (0.52)                      | .26              | 2.07 (0.57)       | 1.67 (0.48)                      | .002 <sup>a</sup> |
| 9    | 3.10 (0.54) | 0.90 (0.37)                      | .02 <sup>a</sup>   | 2.57 (0.53) | 0.73 (0.30)                      | .02 <sup>a</sup>  | 3.00 (0.51) | 1.03 (0.44)                      | .02 <sup>a</sup>  | 2.93 (0.57) | 0.67 (0.51)                      | .20              | 2.80 (0.56)       | 0.93 (0.43)                      | .04 <sup>a</sup>  |
| 10   | 3.03 (0.54) | 0.97 (0.41)                      | .03 <sup>a</sup>   | 2.67 (0.52) | 0.63 (0.35)                      | .08               | 3.03 (0.48) | 1.00 (0.43)                      | .03 <sup>a</sup>  | 3.00 (0.54) | 0.60 (0.47)                      | .22              | 2.50 (0.53)       | 1.23 (0.50)                      | .02 <sup>a</sup>  |
| 11   | 2.93 (0.54) | 1.07 (0.39)                      | .009 <sup>a</sup>  | 2.77 (0.55) | 0.53 (0.31)                      | .10               | 3.60 (0.53) | 0.43 (0.47)                      | .37 <sup>a</sup>  | 2.93 (0.55) | 0.67 (0.47)                      | .17              | 2.20 (0.56)       | 1.53 (0.50)                      | .004 <sup>a</sup> |
| 12   | 3.07 (0.59) | 0.93 (0.42)                      | .03 <sup>a</sup>   | 2.40 (0.57) | 0.53 (0.22)                      | .008 <sup>a</sup> | 3.20 (0.58) | 0.83 (0.58)                      | .16               | 3.00 (0.58) | 0.60 (0.44)                      | .18              | 1.97 (0.57)       | 1.77 (0.52)                      | .002 <sup>a</sup> |

<sup>a</sup>p < .05 compared with week 1.

<sup>b</sup>p < .001 compared with week 1.

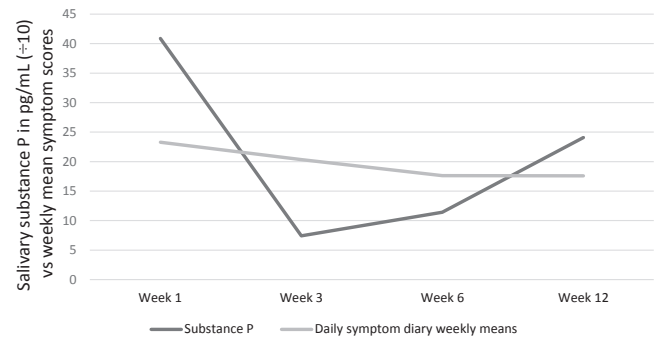


**Figure 3.** Changes in substance P vs changes in symptoms.

point at which SP significantly decreased was 18 to 24 hours after the first acupuncture treatment in week 1, from a mean (SE) of 408.74 (299.12) pg/mL to 90.77 (22.54) pg/mL ( $P = .04$ ); however, the first significant decrease in weekly symptom score was not seen until week 3 (Table 2 and Table 6). SP reached its lowest point in week 3 but then increased again in weeks 6 and 12, while symptoms were continuing to decrease (Fig 3). The role of SP in allergic rhinitis merits further investigation.

In the real acupuncture group, nasal itch, eye itch, sneezing, runny nose, and unrefreshed sleep improved significantly (Table 5). Nasal itch, eye itch, and sneezing are all symptoms that are largely mediated by the transient receptor potential vanilloid 1 (TRPV1).<sup>33–35</sup> This finding suggests that acupuncture may modulate TRPV1 expression, sensitivity, and/or activation.<sup>36</sup> Reductions in rhinorrhea and unrefreshed sleep were probably not associated with TRPV1 modulation.

There was a significant negative correlation between PNIF and MITO at week 12 (correlation coefficient =  $-0.412$ ;  $P = .001$ ) but not at week 0 or week 9 (Table 6). However, when all recruited participants at week 0 were included in the analysis ( $n = 149$ ) (as opposed to only those who completed the study [ $n = 110$ ]), a significant negative correlation was seen (correlation coefficient =  $-0.220$ ;  $P = .004$ ). Moderate to strong correlation among different objective techniques to measure nasal airway patency has been previously reported.<sup>37</sup>

There was a significant positive correlation between Mini-RQLQ nasal symptom domain scores and iTNSSs at week 0 (correlation coefficient =  $0.484$ ;  $P = .001$ ), at week 9 (correlation coefficient =  $0.541$ ;  $P = .001$ ), and at week 12 (correlation coefficient =  $0.484$ ;  $P = .001$ ) (Table 6). A moderate correlation has been reported among different subjective techniques of measuring nasal obstruction.<sup>37</sup> One notable difference between the outcomes produced by the iTNSS and the Mini-RQLQ nasal symptom domain score can be seen in the time point comparisons. The iTNSS revealed significant improvements in nasal symptoms from baseline at week 9 and week 12 only in the real acupuncture group and not in the sham group. However, the Mini-RQLQ revealed significant improvements in nasal symptoms from baseline at week 9 and week 12 in both the real acupuncture and sham acupuncture groups (Table 3).

There was no correlation between objective measures of nasal patency and subjective measures of perceived nasal obstruction at any time point (Table 6). Lack of correlation between objective and subjective measures of nasal obstruction has been previously reported.<sup>37–40</sup> A complex interaction among psychological, neurologic, and mucosal factors appears to be involved in subjective sensations of nasal obstruction.<sup>38</sup> In studies of allergic rhinitis, it is valuable to include both objective and subjective measures of nasal obstruction because they appear to provide different information.<sup>37–40</sup>

Although statistically significant improvements in symptoms and quality of life and reduced use of relief medication were

**Table 6**  
Correlation Coefficients for Objective and Subjective Measurements of Nasal Obstruction

|              | Week 0                   |                          |                          |              | Week 9 |      |       |              | Week 12 |      |       |              |
|--------------|--------------------------|--------------------------|--------------------------|--------------|--------|------|-------|--------------|---------|------|-------|--------------|
|              | MITO                     | PNIF                     | iTNSS                    | MRQLQ stuffy | MITO   | PNIF | iTNSS | MRQLQ stuffy | MITO    | PNIF | iTNSS | MRQLQ stuffy |
| Week 0       |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         | –0.137 ( <i>P</i> = .17) |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        | –0.007 ( <i>P</i> = .94) | –0.137 ( <i>P</i> = .17) |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy | –0.001 ( <i>P</i> = .99) | –0.006 ( <i>P</i> = .52) | –0.007 ( <i>P</i> = .94) |              |        |      |       |              |         |      |       |              |
| Week 9       |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| Week 12      |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| Week 0       |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| Week 9       |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| Week 12      |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MITO         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| PNIF         |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| iTNSS        |                          |                          |                          |              |        |      |       |              |         |      |       |              |
| MRQLQ stuffy |                          |                          |                          |              |        |      |       |              |         |      |       |              |

Abbreviations: iTNSS, instantaneous total nasal symptom score; MITO, mean inferior turbinate obstruction; MRQLQ stuffy – Mini-Rhinoconjunctivitis Quality of Life Questionnaire stuffy nose/blocked nose score; PNIF, peak nasal inspiratory flow.

observed after acupuncture, no statistically significant reductions in nasal airway clearance were seen. Because a previous study found that acupuncture-induced improvements in nasal airways begin to deteriorate 15 minutes after treatment, it is possible that changes in nasal patency may not have been captured at 1-week and 4-week follow-up.<sup>41</sup>

Significant positive correlations between daily symptom diary and daily medication diary mean weekly scores were seen only at week 10 (correlation coefficient = 0.396; *P* = .023) in the sham acupuncture group and at week 5 (correlation coefficient = 0.440; *P* = .02) and week 6 (correlation coefficient = 0.393; *P* = .03) in the real acupuncture group. This finding suggests that medication use, as a behavior, was influenced by factors other than the perceived severity of symptoms. Reduction in the use of relief medications has previously been used in allergic rhinitis studies as a measure of clinical improvement; however, it may not be a reliable outcome measure unless it is placed in context with other subjective and objective measures of clinical status.<sup>9,42</sup>

### Limitations

Potential bias may have occurred in the study because of sex, age, disease, randomization bias, and negative bias due to a sham protocol that was not inert. The convenience sample for the study was 73.6% female; however, in 2012, it was estimated that 51.8% of Australian patients with allergic rhinitis were female.<sup>43</sup> The age group from 18 to 45 years old in the study represents less than 63.2% of the total population of Australians with allergic rhinitis.<sup>43</sup> The study excluded adults with asthma, but it is estimated that 40% of those with allergic rhinitis also have asthma and as many as 80% to 95% of those with allergic asthma have concomitant rhinitis.<sup>44</sup> Nine individuals who completed the study in the no acupuncture group reenrolled and were randomized to either the real or sham acupuncture groups but not to the no acupuncture group again. Of these 9 individuals, 7 completed the study, which represented 6.4% of the total participants in the study, so any bias from randomization would probably be small.

It is also likely that the use of a penetrating needle sham protocol may have introduced a negative bias into the study outcomes. The sham acupuncture protocol used in this study was found to be credible to participants but not inert. The use of sham acupuncture protocols that are not inert can lead to underestimation of the effect size of real acupuncture.<sup>31</sup>

Placebo and/or nocebo responses cannot adequately account for the effects of sham acupuncture in this study because the exit debrief questionnaire indicated that expectation and belief were almost identically distributed between the real and sham acupuncture groups (Table 7). Because differences between time points within the real acupuncture group were statistically significant, but there were no significant differences between groups for total IgE or dust mite specific IgE, it is possible that the study was underpowered to detect significant differences in these biomarkers.

**Table 7**

Exit Debrief Questionnaire: Results for the Real and Sham Acupuncture Groups

| Group            | No.             | Thought real group, No. (%) | Thought sham group, No. (%) | Undecided, No. (%) |
|------------------|-----------------|-----------------------------|-----------------------------|--------------------|
| Real acupuncture | 37 <sup>a</sup> | 17 (45.9)                   | 18 (48.6)                   | 2 (5.4)            |
| Sham acupuncture | 35              | 17 (48.6)                   | 16 (45.7)                   | 2 (5.7)            |

<sup>a</sup>An error occurred in the labeling of one of the envelopes. There were only 36 participants in the real acupuncture group and 37 in the sham acupuncture treatment. One sham acupuncture participant has been mislabeled as belonging to the real acupuncture group. This error would have had little effect on the outcomes.

The decision to use salivary analyses in this study was based on previous work that suggested that saliva might provide a proxy for upper airways with less discomfort and easier access than sampling nasal fluids.<sup>5</sup> In future studies it is recommended that other technologies, such as ELISpot, T-cell cones, or Nanostring analysis, may provide a more accurate measure of cellular or tissue-level modulation.

## Conclusions

Acupuncture treatment for persistent allergic rhinitis appeared to have a significant effect in decreasing the total IgE and allergen specific IgE for house dust mite, which persisted at 4-week follow-up. A significant down-regulation was also seen in SP, but the course of this decrease did not correlate with the course of improvements in symptoms and quality of life. Symptoms and quality of life improved significantly and were still continuing to improve 4 weeks after treatment ceased. Evidence of immunomodulation after acupuncture in allergic rhinitis may also have relevance to other allergic conditions, such as allergic asthma.

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