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# Acupuncture in Patients with Allergic Asthma: A Randomized Pragmatic Trial

Benno Brinkhaus, MD,[1] Stephanie Roll, PhD,[1] Susanne Jena, PhD,[2] Katja Icke,[1] Daniela Adam, MA,[1] Sylvia Binting,[1] Fabian Lotz,[1] Stefan N. Willich, MD, MPH,[1] and Claudia M. Witt, MD, MBA[1,3]

**Abstract**

***Background:*** Although the available evidence is insufficient, acupuncture is used in patients suffering from chronic asthma. The aim of this pragmatic study was to investigate the effectiveness of acupuncture in addition to routine care in patients with allergic asthma compared to treatment with routine care alone.

***Methods:*** Patients with allergic asthma were included in a randomized controlled trial and randomized to receive up to 15 acupuncture sessions over 3 months or to a control group receiving routine care alone. Patients who did not consent to randomization received acupuncture treatment for the first 3 months and were followed as a cohort. All trial patients were allowed to receive routine care in addition to study treatment. The primary endpoint was the asthma quality of life questionnaire (AQLQ, range: 1–7) at 3 months. Secondary endpoints included general health related to quality of life (Short-Form-36, SF-36, range 0–100). Outcome parameters were assessed at baseline and at 3 and 6 months.

***Results:*** A total of 1,445 patients (mean age 43.8 [SD 13.5] years, 58.7% female) were randomized and included in the analysis (184 patients randomized to acupuncture and 173 to control, and 1,088 in the nonrandomized acupuncture group). In the randomized part, acupuncture was associated with an improvement in the AQLQ score compared to the control group (difference acupuncture vs. control group 0.7 [95% confidence interval (CI) 0.5–1.0]) as well as in the physical component scale and the mental component scale of the SF-36 (physical: 2.5 [1.0–4.0]; mental 4.0 [2.1–6.0]) after 3 months. Treatment success was maintained throughout 6 months. Patients not consenting to randomization showed similar improvements as the randomized acupuncture group.

***Conclusions:*** In patients with allergic asthma, additional acupuncture treatment to routine care was associated with increased disease-specific and health-related quality of life compared to treatment with routine care alone.

**Keywords:** acupuncture, allergic asthma, routine care, complementary medicine, randomized controlled trial, pragmatic trial, comparative effectiveness research

## Introduction

Asthma is a major health problem associated with significant morbidity and mortality. The prevalence of asthma in adults ranges from 4% to 32% in different countries.[1] Corticosteroids continue to be the treatment of choice for mild to moderate asthma, but limited compliance with daily inhaled medication is a major problem.[2] A reasonable estimate is that about 30% of adults and 60% of children in the U.S. use some form of complementary and integrative medicine (CIM) therapy for their asthma.[3]

In China, herbal medicine and acupuncture have traditionally been utilized in the treatment of lung disease, including asthma. In Western countries such adjunct treatment

[1]Institute for Social Medicine, Epidemiology and Health Economics, Charité Universitätsmedizin Berlin, Berlin, Germany.
[2]Department for Medical Statistics and Informatics, Universität Freiburg, Freiburg, Germany.
[3]Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland.

in asthma was used too.[4] However, several studies in the last two decades that evaluated the efficacy of acupuncture in the treatment of asthma have been inconclusive.[5–10] More research in this area has been encouraged.[11–14] Additionally, most trials compared acupuncture with sham acupuncture to further investigate the specific benefit. However, Comparative Effectiveness Research, which focuses on real life evidence and aims to inform clinical and health policy decision making, has also gained relevance in the last few years.[15]

Under increasing budgetary pressure, the Federal Committee of Physicians and Health Insurers in Germany recommended that large research projects (so called ''*Modellvorhaben Akupunktur*'') should be conducted to evaluate the effectiveness of acupuncture in specific chronic diseases, especially in pain diseases. Initially, chronic asthma was included in the research.[16] Therefore, acupuncture could only be reimbursed by insurance companies if patients were treated with acupuncture by physicians who participated in one of the studies.

The primary objective of the present study was to investigate the effectiveness of acupuncture in combination with routine care on disease-specific and health-related quality of life in patients with allergic asthma compared to routine care alone. Also investigated were the effects of acupuncture in randomized versus nonrandomized patients, the impact of time on treatment effect, and the possible contribution of specific patient and/or physician characteristics to treatment outcomes.

## Methods

### *Design*

The Acupuncture in Routine Care (ARC Asthma) Study was a multi-center, randomized, controlled, pragmatic trial including a nonrandomized cohort in patients with allergic asthma (Fig. 1). Patients who agreed to randomization were allocated to an acupuncture group that received immediate acupuncture treatment or to a control group whose acupuncture treatment was introduced after 3 months. All patients who declined to be randomized were included in a third arm and received immediate acupuncture treatment (nonrandomized acupuncture group). The study period per patient was 6 months and was comprised of a 3-month treatment phase followed by 3 months of follow-up. The control group received acupuncture after the 3-month primary endpoint too. This was done improve patient recruitment, because all patients receive acupuncture within the trial and to motivate patients to fill in the study questionnaires.

The ARC asthma study was part of a large acupuncture research initiative of a group of social health insurance funds which provide coverage to ~10% of the German population. The protocol of the ARC asthma study was approved by the respective local ethics review boards, and the study was performed according to common guidelines (Declaration of Helsinki, Good Epidemiological Practice www.dundee.ac.uk/iea/GoodPract.htm). All study participants provided written, informed consent. The trial registration number is DRKS00009621.

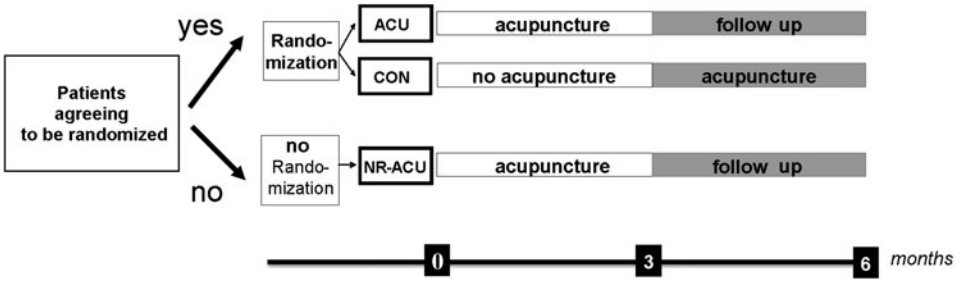
### *Patients*

After contacting a participating physician who treated chronic asthma, patients insured by one of the participating social health insurance funds were recruited. Patients were informed about the study if they requested acupuncture or if the physician considered acupuncture to be an adequate treatment. Patients of any gender considered for inclusion were at least 18 years old and carried a clinical diagnosis of allergic asthma for more than 6 months, with mild to moderate symptoms requiring treatment. Patients with other forms of obstructive lung diseases and severe pulmonary diseases were excluded from the study.

Using a central telephone randomization procedure, we used block randomization (the block lengths of 10 were blinded to the study centers) and an allocation ratio of 1:1 (random list generated with SAS [SAS, Inc., Cary, NC]). Patients who declined randomization were included in the nonrandomized acupuncture cohort group. Patients were only included in the study if we received both the physician baseline questionnaire, including the main data information about each patient and his/her disease, and the patient consent form following randomization. Upon successful study inclusion, patients were sent the baseline questionnaire by mail.

### *Interventions*

Study physicians were all medical doctors (MD) with different medical specializations and listed as registered acupuncture specialists participating in this acupuncture project. Study physicians had at least an A-diploma, which represents a minimum of 140 h of certified acupuncture




| Patient Evaluation | Baseline | 3-month | 6-month |
|---|---|---|---|
| AQLQ | X | X | X |
| SF-36 | X | X | X |
| General judgment | | X | 0 |

**FIG. 1.** Study design including patient evaluation.

education (Supplementary Table S1; Supplementary materials are available online at www.liebertpub.com/acm). This education and other training include wide variations in style and acupuncture technique in Germany.

Patients in both the randomized and nonrandomized groups received up to 15 acupuncture sessions during the first 3 months and no acupuncture between 3 and 6 months. The aim was to assess the effectiveness of acupuncture in general medical practice. Treatment, including the number of needles used and sites of needle placement, was left to the physicians' discretion. Only disposable, single-use needles were allowed. In addition, only manual needle stimulation was allowed, whereas other forms of acupuncture treatment (e.g., laser acupuncture, electro-acupuncture, moxibustion) were excluded. The control group was asked not to use any kind of acupuncture during the first 3 months, but they could receive acupuncture by the study physicians, who were reimbursed by the participating health insurance companies. In all study groups, patients were allowed to use any additional conventional treatments as routine care.

Participating health insurance companies assumed 100% of acupuncture costs for patients who agreed to randomization and 90% of costs for patients who participated in the study, but did not agree to randomization.

### *Outcome measurements*

All patients were required to complete standardized questionnaires (including socio-demographic characteristics) at baseline and at 3-month intervals for the duration of the study. The primary outcome measure was the asthma quality of life questionnaire (AQLQ[17]) three months after randomization. The AQLQ measures the disease-specific quality of life and contains 32 items in 5 domains (strenuous exercise, moderate exercise, work-related activities, social activities, and sleep). The AQLQ results are presented as sum score (range 1–7) with the higher values indicating higher disease-specific quality of life.

Improvement of AQLQ score (treatment responders) was used as a secondary outcome because the absolute improvement was less correlated to baseline than the relative improvement ($r = -0.480$ vs. $r = -0.581$). A change in the AQLQ score greater than 0.5 was considered clinically significant[18] and those patients were considered to be treatment responders. All patients without data were counted as nonresponders.

Secondary outcome parameters included the SF-36 (Short-Form-36) component scales and its sub-scores to assess health-related quality of life[19,20] 3 and 6 months after study initiation (range: 0–100, higher values indicating higher quality of life). Further secondary outcome parameters included satisfaction with treatment and treatment success after 3 months, on a 10-point scale (0–no success/completely unsatisfied; 10 = complete success/very satisfied).

The health insurance companies provided data about co-interventions. Side effects were evaluated using patient and physician questionnaires after 3 months. To study the maintenance of therapeutic success in the acupuncture groups and the effect of delayed acupuncture treatment in the control group, changes from baseline to 6 months were calculated analogously.

### *Statistics*

Covariance analyses with adjustments for the respective baseline values to analyze the primary and continuous secondary outcomes were applied. For the primary outcome, we tested the null hypothesis: Mean AQLQ after 3 months of the acupuncture group is equal to the mean AQLQ after three months in the control group. The acupuncture and the control groups were compared similarly for secondary outcomes. The hypotheses of the comparison between the randomized and nonrandomized patients were tested analogue the hypothesis above. For the analyses for the primary and secondary outcomes were based on intention-to-treat population using the largest available data set. Sensitivity analyses were performed for the primary outcome by using various hot-deck methods or regression-based multiple imputations.

To identify factors that affect improvements in the AQLQ score and to analyze the patient selection, we fitted a linear mixed model for the AQLQ score to the data of all study patients in a first step. A mixed model with the patient's physician as random effect was chosen to comply with the potential cluster structure of the data because several patients were included by the same physician and thus may reveal more similarity in their responses to treatment than patients treated by different physicians. The chosen mixed model corrects for these cluster effects. We prespecified several characteristics of the physicians (age, years of professional experience, type of acupuncture, diploma, hours of acupuncture training, years of acupuncture experience, diagnosis in the context of Chinese medicine, and percentage of practice time with acupuncture treatment) and of the patients (sex, age, less or more than 10 years of education, baseline physical and mental quality-of-life scores, baseline AQLQ score, the duration of complaints before the study, and the study group to which each patient was assigned) before the study started and included these variables as fixed effects in the mixed model. In a second step, we selected significant variables in a stepwise backwards procedure, based on likelihood ratio tests and reported the corresponding $p$-values. In a third step, we added the corresponding interaction terms between the selected regressors and the treatment group to the model, with backwards selection if the terms were significant to specify the final model. Differences between physicians were judged on the basis of Wald tests of the between-physician variance component. All reported $p$-values are based on two-directional alternatives to the respective null hypotheses. The significance level of each test procedure was $\alpha = 5\%$. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. and SAS/STAT Software Version 9.4 (Copyright SAS Institute, Inc. SAS and all other SAS Institute, Inc. product or service names are registered trademarks or trademarks of SAS Institute, Inc., Cary, NC) were used.

## Results

### *Patient inclusion, baseline characteristics and treatment*

A total of 1,445 allergic asthma patients were recruited by 992 study physicians (Fig. 2). A total of 357 patients had accepted randomization and were allocated to acupuncture ($n = 184$) or control group ($n = 173$), but 16 patients in the acupuncture group and 12 in the control group did not return their 3-month questionnaires. Altogether, 74 patients (38 acupuncture, 36 control) could not be included in the analysis because they didn't send back the questionnaire or have a complete dataset for the AQLQ at three months. At 6

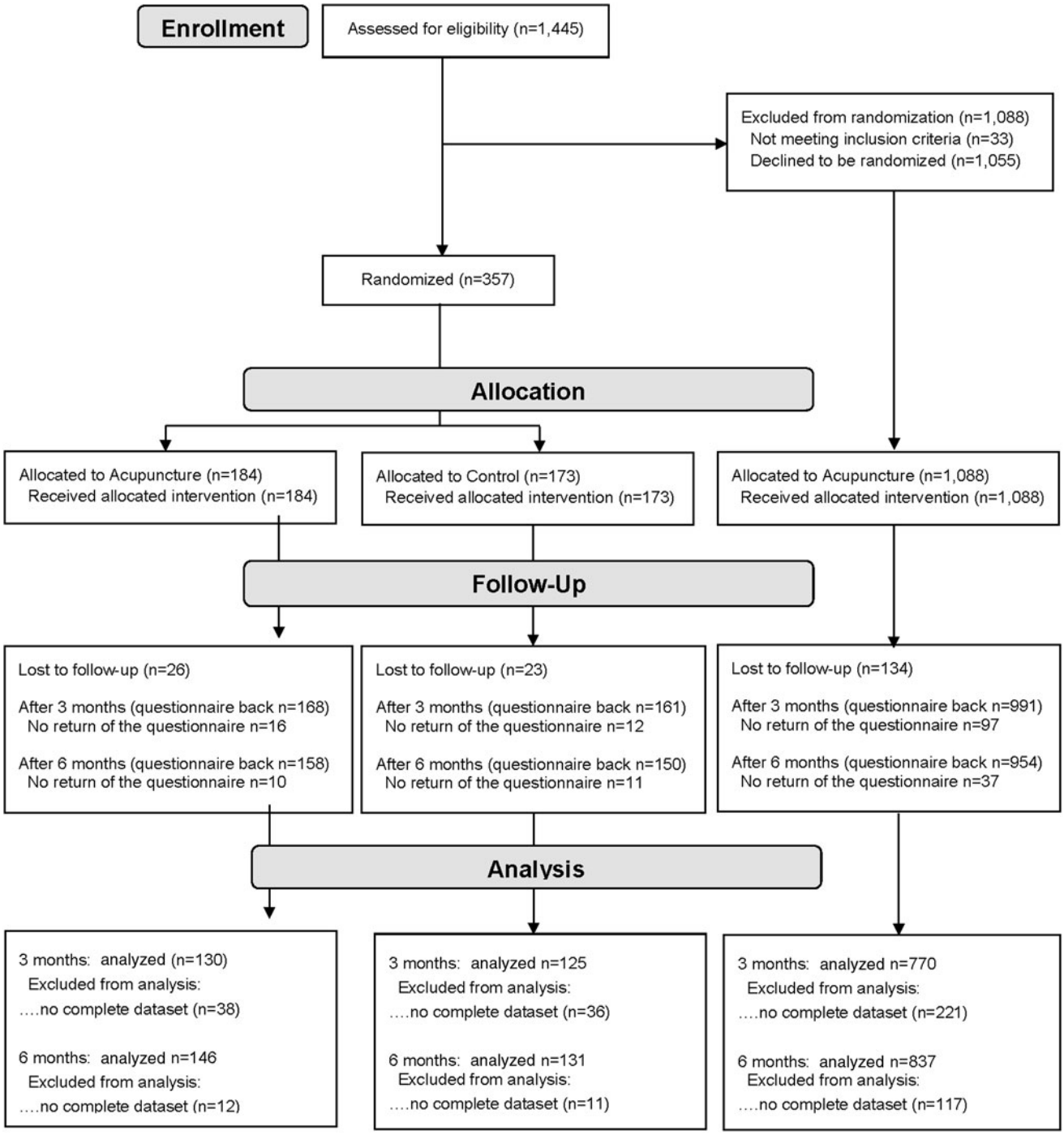



**FIG. 2.** Trial flowchart. AQLQ, asthma quality of life questionnaire.

months, 13 patients (12 acupuncture, 11 control) were excluded from the analysis, however we did not collect 6-month questionnaires from participants who did not send us the 3-month questionnaires.

The remaining 1,025 patients (130 acupuncture, 125 control, 770 nonrandomized-acupuncture) were included in the analysis after 3 months (data available for 71% of the patients; 71% acupuncture, 72% control, 71% nonrandomized acupuncture).

The randomized groups were comparable with regard to the baseline characteristics within the randomized groups and between the randomized and non-randomized acupuncture groups (Table 1). Patients in the acupuncture groups received $10.8 \pm 3.0$ acupuncture sessions (randomized acupuncture $10.5 \pm 3.1$; nonrandomized acupuncture $10.9 \pm 3.0$; $p = 0.096$). Most patients (71%) received 5–10 sessions, whereas 27% received more than 10 sessions and 3% received less than 5 sessions.

### *Randomized comparisons*

Over 3 months, the AQLQ improved by a mean of 1.1 (95% confidence interval [CI] 0.9–1.2) in the randomized

Table 1. Baseline Characteristics of Study Population

| | *Randomized groups* | | *Acupuncture groups* | | *Total* |
|---|---|---|---|---|---|
| | *Acupuncture* n = *184* *mean ± SD*/n *(%)* | *Control* n = *173* *mean ± SD*/n *(%)* | *Randomized* n = *184* *mean ± SD*/n *(%)* | *Nonrandomized* n = *1,088* *mean ± SD*/n *(%)* | N = *1,445* *mean ± SD*/ n *(%)* |
| Female | 106 (57.6) | 99 (57.2) | 106 (58) | 643 (59.1) | 848 (58.7) |
| Age (years) | 43.5 ± 12.4 | 44.1 ± 14.1 | 43.5 ± 12.4 | 43.8 ± 13.5 | 43.8 ± 13.5 |
| >10 years of school | 78 (45.9) | 79 (48.5) | 78 (46) | 539 (53.7) | 696 (52.1) |
| Disease duration (years) | 13.9 ± 12.7 | 12.4 ± 11.7 | 13.9 ± 12.7 | 12.5 ± 11.0 | 12.7 ± 13.3 |
| Conc. allergic rhinitis | 138 (75.0) | 122 (73.1) | 138 (75.0) | 842 (77.4) | 1,1 (77.4) |
| Severity score Grade 1 | 45 (24.5) | 44 (25.6) | 45 (24.5) | 315 (29.1) | 404 (28.1) |
| Severity score Grade 2 | 78 (42.4) | 70 (40.7) | 78 (42.4) | 460 (42.5) | 608 (42.3) |
| Severity score Grade 3 | 43 (23.4) | 44 (25.6) | 43 (23.4) | 240 (22.2) | 327 (22.7) |
| Severity score Grade 4 | 18 (9.8) | 14 (8.1) | 18 (9.8) | 68 (6.3) | 100 (6.9) |
| CIM last 12 months | 39 (21.4) | 39 (23.1) | 39 (21.4) | 298 (26.8) | 376 (27.0) |
| Acupuncture last 12 months | 22 (12.1) | 18 (10.6%) | 22 (12.1) | 159 (15.1) | 199 (14.2) |
| AQLQ | | | | | |
| Global score | 4.3 ± 1.1 | 4.5 ± 0.9 | 4.3 ± 1.1 | 4.2 ± 1.1 | 4.3 ± 1.1 |
| Symptoms | 4.2 ± 1.3 | 4.3 ± 1.1 | 4.2 ± 1.3 | 4.1 ± 1.2 | 4.1 ± 1.2 |
| Activities | 4.5 ± 1.2 | 4.6 ± 1.0 | 4.5 ± 1.2 | 4.4 ± 1.2 | 4.4 ± 1.2 |
| Emotions | 4.3 ± 1.4 | 4.4 ± 1.3 | 4.3 ± 1.4 | 4.2 ± 1.3 | 4.2 ± 1.3 |
| Environment | 4.6 ± 1.3 | 4.7 ± 1.1 | 4.6 ± 1.3 | 4.6 ± 1.3 | 4.6 ± 1.3 |
| Quality of life (SF-36) | | | | | |
| Physical component score | 45.8 ± 9.6 | 46.4 ± 8.5 | 45.8 ± 9.6 | 45.3 ± 9.5 | 45.5 ± 9.4 |
| Mental component score | 43.6 ± 11.0 | 45.3 ± 10.7 | 43.6 ± 11.0 | 44.8 ± 10.6 | 44.7 ± 10.7 |

CIM, complementary and integrative medicine; AQLQ, asthma quality of life questionnaire; Conc., concomitant.

acupuncture group and by 0.4 (95% CI 0.2–0.5) in the control group (Fig. 3). In the primary analyses, the 3-month scores (mean [95% CI]) were 5.5 for the acupuncture group (5.3–5.6) and 4.8 for the control group (4.6–4.9), resulting in a difference of 0.7 (95% CI 0.5–1.0, $p < 0.001$) between groups.

This improvement was robustly demonstrated in the sensitivity analyses for missing data (smallest difference between acupuncture and control group of 0.6 [SE 0.11] [95% CI 0.3–0.8], $p < 0.001$). The proportion of treatment responders was 56.5% in the acupuncture group compared to 26.0% in the control group ($p < 0.001$).

In the AQLQ score and its subscales, the 3-month improvements were significantly greater in the randomized acupuncture group than in the control group with relevant group differences (difference in the AQLQ global score acupuncture vs. control group 0.7 [95% CI 0.5–1.0; $p < 0.001$] (Table 2). Similar results were found for quality of life (on both SF-36 component scales [difference in the physical sum score: 2.5 (1.0–4.0 $p < 0.001$)] and in the mental sum score: 4.0 [2.1–6.0] $p < 0.001$).

During the 3 months following randomization, the use of additional prescribed medication for allergic asthma in the acupuncture group (83.2% of patients) was similar to usage in the control group (83.8%, $p = 0.896$). In addition, there were no differences between the acupuncture and control groups regarding the number of patients who used additional acupuncture (acupuncture group, 21.8% of patients; control group, 20%, $p = 0.756$).

### *Nonrandomized comparisons*

In a comparison between the nonrandomized acupuncture group (AQLQ score 1.2 [95% CI 1.1–1.2]) and the randomized acupuncture group (AQLQ score 1.1 [95% CI 1.0–1.3]; mean difference –0.02 [95% CI: –0.2 to 0.2], $p = 0.859$) at 3 months, improvements to the AQLQ scores were similar.

The proportion of treatment responders was 56.5% in the randomized acupuncture group compared to 57.6% in the nonrandomized acupuncture group ($p = 0.895$). There were no significant differences between randomized and nonrandomized patients in the 3-month improvements from baseline (Table 3).

### *Factors affecting the size of the 3-month AQLQ or quality of life (SF-36)*

Several covariates were considered to affect the 3-month AQLQ score. According to the multivariate analysis consistently over all treatment groups and independent of treatment, increases in AQLQ scores were significantly more pronounced in female patients than in male patients ($p = 0.008$), patients with higher values on the physical ($p = 0.001$) or mental ($p = 0.015$) quality of life scales, in patients where the AQLQ at baseline was more pronounced ($p < 0.001$), and in those that a severity score below 4 ($p = 0.002$). However, the AQLQ score improvement did not differ significantly between the physicians who treated the patients ($p = 0.356$).

After adjustment with the above-mentioned confounding factors (AQLQ at baseline, gender, physical and mental quality of life scores, severity score), the difference of the AQLQ score between acupuncture and control after 3 months were estimated to be 0.7 (difference between acupuncture vs. control 95% CI 0.5–1.1), $p < 0.001$ and therefore similar to the estimates adjusted only with the baseline value.

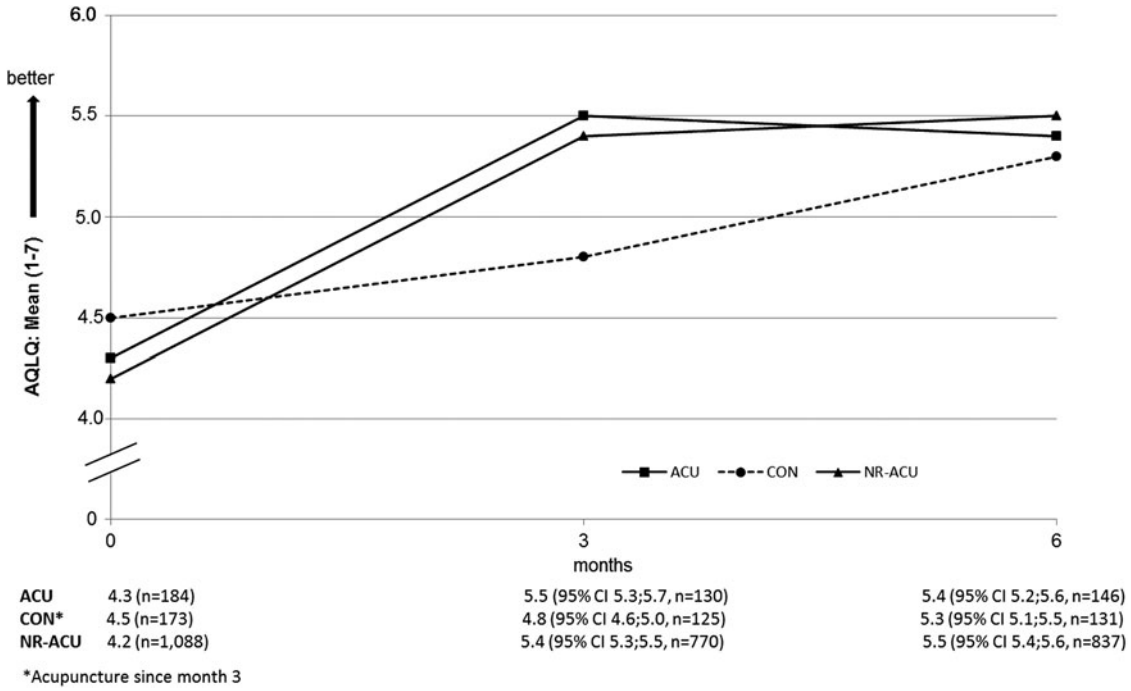



**FIG. 3.** Development of the AQLQ score (means and CI) in the two randomized treatment groups (ACU indicates acupuncture group, CON indicates control group and NR-ACU indicates nonrandomized acupuncture group at baseline, 3 and 6 months). All three groups received routine care, after 3 months the CON received also acupuncture. CI, confidence interval.

There was no significant acupuncture effect modifier. The physician's acupuncture qualification (type of Diploma A or B ($p=0.617$), specialization of the physician ($p=0.463$), Tradition Chinese Medicine (TCM) diagnostics before acupuncture ($p=0.705$), number of sessions ($p=0.698$), years of experience in performing acupuncture ($p=0.858$), age of physician ($p=0.673$), years being a physician ($p=0.138$), hours of acupuncture training ($p=0.609$), amount of practical experience during acupuncture training ($p=0.618$), amount of time of acupuncture during daily practice ($p=0.337$), amount of patients treated with acupuncture during daily practice ($p=0.795$) had no significant influence on the effect of the treatment.

### *Satisfaction with the treatment and the success of treatment*

After 3 months, significant differences emerged between both groups regarding the general judgment of treatment

Table 2. Disease-Specific Quality of Life (AQLQ) and Secondary Outcomes for Randomized Groups (Mean, 95% CI) After 3 Months (Adjusted for Respective Baseline Value)

| | *Randomized groups* | | | | | |
|---|---|---|---|---|---|---|
| | | | | | *Absolute differences to baseline* | |
| | *Acupuncture mean (95% CI)* | *Control mean (95% CI)* | *Acupuncture vs. control* | | *Acupuncture mean difference (95% CI)* | *Control mean difference (95% CI)* |
| | | | *Δ (95% CI)* | p[a] | | |
| AQLQ | | | | | | |
| Global score | 5.5 [5.3–5.6] | 4.8 [4.6–4.9] | 0.7 [0.5–1.0] | <0.001 | 1.1 [0.9–1.2] | 0.4 [0.2–0.5] |
| Symptoms | 5.4 [5.2–5.6] | 4.7 [4.5–4.9] | 0.8 [0.5–1.0] | <0.001 | 1.2 [1.0–1.4] | 0.4 [0.2–0.6] |
| Activities | 5.6 [5.4–5.7] | 4.9 [4.7–5.0] | 0.7 [0.5–0.9] | <0.001 | 1.1 [0.9–1.2] | 0.4 [0.2–0.5] |
| Emotions | 5.5 [5.3–5.7] | 4.7 [4.5–4.9] | 0.8 [0.5–1.1] | <0.001 | 1.2 [1.0–1.4] | 0.4 [0.2–0.6] |
| Environment | 5.4 [5.2–5.5] | 4.8 [4.6–4.9] | 0.6 [0.4–0.8] | <0.001 | 0.8 [0.6–0.9] | 0.1 [–0.0 to 0.3] |
| Quality of life (SF-36) | | | | | | |
| Physical component score | 49.1 [48.1–50.2] | 46.6 [45.5–47.7] | 2.5 [1.0–4.0] | <0.001 | 3.2 [2.1–4.2] | 0.6 [–0.4 to 1.7] |
| Mental component score | 48.7 [47.3–50.0] | 44.6 [43.2–46.0] | 4.0 [2.1–6.0] | <0.001 | 4.3 [2.9–5.6] | 0.3 [–1.1 to 1.7] |
| General judgment[b] | | | | | | |
| Satisfaction by treatment | 8.5 [8.1–8.8] | 7.4 [7.0–7.8] | 1.1 [0.5–1.6] | <0.001 | | |
| Success of treatment | 7.3 [6.8–7.7] | 6.2 [5.7–6.7] | 1.1 [0.4–1.7] | 0.001 | | |

Higher values indicate better status.
[a]*p*-Values from covariance analyses with adjustment for respective baseline value.
[b]General judgment was adjusted with the baseline AQLQ score.
CI, confidence interval; SF-36, 36 item short-form health survey.

Table 3. Disease-Specific Quality of Life and Secondary Outcomes for Acupuncture Groups (Mean, 95% CI) After 3 Months (Adjusted for Respective Baseline Value)

| | *Acupuncture groups* | | | | | |
|---|---|---|---|---|---|---|
| | | | *Randomized vs. nonrandomized* | | *Absolute differences to baseline* | |
| | *Randomized mean (95% CI)* | *Nonrandomized mean (95% CI)* | *Δ (95% CI)* | p[a] | *Randomized mean difference (95% CI)* | *Nonrandomized mean difference (95% CI)* |
| AQLQ | | | | | | |
| Global score | 5.4 [5.3–5.6] | 5.4 [5.4–5.5] | –0.0 [–0.2 to 0.2] | 0.859 | 1.1 [1.0–1.3] | 1.2 [1.1–1.2] |
| Symptoms | 5.4 [5.2–5.5] | 5.4 [5.3–5.5] | –0.0 [–0.2 to 0.2] | 0.768 | 1.3 [1.1–1.5] | 1.3 [1.2–1.4] |
| Activities | 5.5 [5.3–5.7] | 5.5 [5.5–5.6] | –0.0 [–0.2 to 0.2] | 0.879 | 1.1 [0.9–1.3] | 1.1 [1.1–1.2] |
| Emotions | 5.5 [5.3–5.6] | 5.4 [5.3–5.5] | 0.1 [–0.2 to 0.3] | 0.615 | 1.3 [1.1–1.4] | 1.2 [1.1–1.3] |
| Environment | 5.4 [5.2–5.6] | 5.4 [5.4–5.5] | –0.0 [–0.2 to 0.1] | 0.649 | 0.8 [0.6–0.9] | 0.8 [0.7–0.9] |
| Quality of life (SF-36) | | | | | | |
| Physical component score | 48.7 [47.7–49.8] | 49.3 [48.9–49.7] | –0.6 [–1.7 to 0.5] | 0.299 | 3.4 [2.4–4.5] | 4.0 [3.6–4.4] |
| Mental component score | 48.9 [47.6–50.2] | 49.0 [48.5–49.5] | –0.1 [–1.5 to 1.3] | 0.844 | 4.1 [2.8–5.4] | 4.2 [3.7–4.8] |
| General judgment[b] | | | | | | |
| Satisfaction by treatment | 8.5 [8.2–8.8] | 8.3 [8.2–8.4] | 0.2 [–0.2 to 0.6] | 0.288 | | |
| Success of treatment | 7.3 [6.9–7.7] | 7.4 [7.3–7.6] | –0.1 [–0.6 to 0.3] | 0.547 | | |

[a]*p*-Values from covariance analyses with adjustment for respective baseline value.
[b]General judgment was adjusted with the baseline AQLQ score.

satisfaction ($p<0.001$) and treatment success ($p=0.001$) favoring the acupuncture treatment compared to the waiting list control group, whereas there were no significant differences between acupuncture groups for both variables (Table 2).

### *Durability of acupuncture effects over 6 months*

The 6-month improvements in the randomized and nonrandomization groups were comparable to the 3 months' improvements (Tables 4 and 5). The 6-month treatment responder rates in the randomized and nonrandomized acupuncture groups were 54.6% and 57.5%, respectively ($p=0.640$).

### *Delayed acupuncture*

Delayed acupuncture in the control group between months 3 and 6 resulted in the same AQLQ improvement as compared to earlier acupuncture in the acupuncture group after 6 months (Table 5). Following delayed acupuncture, the improvement in AQLQ seen in control patients after 6 months was comparable to that improvement observed after 3 months in patients who had been randomized to immediate acupuncture therapy (Fig. 3).

### *Side effects*

In 11.5% of cases ($n=134$), a total of 138 side effects were reported after receiving acupuncture in the randomized and nonrandomized acupuncture groups in the first 3 months and in the control group after receiving acupuncture in months 3–6, including 75%, ($n=104$) minor local bleeding or haematoma, 5% ($n=7$) pain for example, needling pain, 3% ($n=4$) vegetative symptoms such as sweating, blood pressure decrease, or dizziness and 17% ($n=23$) other. No life-threatening side effects were reported.

Table 4. Disease-Specific Quality of Life and Secondary Outcomes for Randomized Groups (Mean, 95% CI) After 6 Months (Adjusted for Respective Baseline Value)

| | *Randomized groups* | | | | | |
|---|---|---|---|---|---|---|
| | | | *Acupuncture vs. control* | | *Absolute differences to baseline* | |
| | *Acupuncture mean (95% CI)* | *Control mean (95% CI)* | *Δ (95% CI)* | p[a] | *Acupuncture mean difference (95% CI)* | *Control mean difference (95% CI)* |
| AQLQ | | | | | | |
| Global score | 5.4 [5.2–5.5] | 5.3 [5.2–5.5] | 0.1 [–0.2 to 0.3] | 0.638 | 1.0 [0.8–1.1] | 0.9 [0.8–1.1] |
| Symptoms | 5.3 [5.2–5.5] | 5.3 [5.1–5.5] | 0.0 [–0.2 to 0.3] | 0.748 | 1.1 [0.9–1.3] | 1.1 [0.9–1.2] |
| Activities | 5.5 [5.3–5.6] | 5.4 [5.2–5.5] | 0.1 [–0.1 to 0.3] | 0.431 | 0.9 [0.8–1.1] | 0.9 [0.7–1.0] |
| Emotions | 5.4 [5.2–5.6] | 5.3 [5.1–5.5] | 0.1 [–0.2 to 0.3] | 0.626 | 1.1 [0.9–1.2] | 1.0 [0.8–1.2] |
| Environment | 5.3 [5.1–5.4] | 5.3 [5.2–5.5] | –0.1 [–0.3 to 0.2] | 0.588 | 0.6 [0.5–0.8] | 0.7 [0.5–0.9] |
| Quality of life (SF-36) | | | | | | |
| Physical component score | 49.1 [48.0–50.1] | 49.2 [48.1–50.3] | –0.2 [–1.7 to 1.4] | 0.844 | 3.2 [2.2–4.3] | 3.4 [2.3–4.5] |
| Mental component score | 49.8 [48.5–51.1] | 48.0 [46.6–49.3] | 1.8 [–0.0 to 3.7] | 0.056 | 5.1 [3.8–6.4] | 3.3 [1.9–4.7] |

[a]*p*-Values from covariance analyses with adjustment for respective baseline value.

Table 5. Disease-Specific Quality of Life and Secondary Outcomes for Acupuncture Groups (Mean, 95% CI) After 6 Months (Adjusted for Respective Baseline Value)

| | *Acupuncture groups* | | | | | |
|---|---|---|---|---|---|---|
| | | | *Randomized vs. nonrandomized* | | *Absolute differences to baseline* | |
| | *Randomized mean (95% CI)* | *Nonrandomized mean (95% CI)* | *Δ (95% CI)* | p[a] | *Randomized mean difference (95% CI)* | *Nonrandomized mean difference (95% CI)* |
| AQLQ | | | | | | |
| Global score | 5.3 [5.1–5.5] | 5.5 [5.4–5.6] | –0.2 [–0.4 to –0.0] | 0.027 | 1.1 [0.9–1.2] | 1.3 [1.2–1.3] |
| Symptoms | 5.3 [5.1–5.4] | 5.5 [5.4–5.6] | –0.2 [–0.4 to –0.0] | 0.022 | 1.2 [1.0–1.4] | 1.4 [1.4–1.5] |
| Activities | 5.4 [5.2–5.6] | 5.6 [5.5–5.6] | –0.2 [–0.3 to 0.0] | 0.074 | 1.0 [0.8–1.2] | 1.2 [1.1–1.2] |
| Emotions | 5.3 [5.1–5.5] | 5.5 [5.5–5.6] | –0.2 [–0.4 to –0.0] | 0.036 | 1.1 [0.9–1.3] | 1.4 [1.3–1.4] |
| Environment | 5.2 [5.1–5.4] | 5.4 [5.3–5.5] | –0.2 [–0.4 to 0.0] | 0.059 | 0.6 [0.5–0.8] | 0.8 [0.7–0.9] |
| Quality of life (SF-36) | | | | | | |
| Physical component score | 48.8 [47.7–49.9] | 49.9 [49.4–50.4] | –1.1 [–2.3 to 0.1] | 0.083 | 3.4 [2.3–4.5] | 4.5 [4.0–5.0] |
| Mental component score | 49.8 [48.5–51.1] | 48.6 [48.0–49.1] | 1.3 [–0.2 to 2.7] | 0.081 | 5.2 [3.9–6.5] | 4.0 [3.4–4.5] |

[a]*p*-Values from covariance analyses with adjustment for respective baseline value.

## Discussion

In this pragmatic randomized trial, allergic asthma patients treated with acupuncture in addition to routine care showed clinically significant improvements in disease-specific and general quality of life compared to patients who received routine care alone. In addition, treatment outcomes after acupuncture were better compared in patients who declined randomization compared to those patients who were randomized in the control group. However, physician characteristics, such as level of acupuncture training or certification and experience with acupuncture administration, did not influence treatment outcomes significantly.

To our knowledge, the present study is the largest randomized trial of acupuncture in allergic asthma to date, including about 5% of physicians specializing in acupuncture in Germany. Following the methods of Comparative Effectiveness Research, this randomized study took a pragmatic approach,[21] aiming to evaluate acupuncture in a manner that would reflect as closely as possible the conditions of routine medical practice (needle acupuncture and manual stimulation) and to maximize external validity. Therefore, the results of this trial are clinically relevant and have great importance for decision makers in the healthcare system. Internationally established and accepted outcome parameters were used to evaluate patients with allergic asthma.[17] In addition, this study had relatively high follow-up rates and conservative methods were used to account for missing data. The addition of a third study arm, which included patients who declined randomization, allowed for the investigation of potential selection effects.

However, such a pragmatic approach also has methodological limitations: Neither patients nor study physicians were blinded to treatment in this study. Because the patients assessed all outcome parameters independently, patient bias toward the intervention cannot be generally ruled out. To minimize social acceptability bias, all questionnaires were sent directly from and to the coordinating research institute. Because both the specifics of acupuncture treatment as well as of any co-interventions were left to the discretion of the study physicians, the treatment regimens of patients in the study were highly variable. Inclusion criteria were broad, which resulted in a heterogeneous patient sample with some possible diagnostic misclassification. While these issues might be considered limitations from an experimental perspective, including a minor internal validity, the study design was chosen to simulate general medical practice as closely as possible and therefore to yield a high external validity.

Patients' self-selection in randomized studies of CIM could be a relevant problem.[22] Therefore, to control for selection bias, the use of study designs that also include nonrandomized patients appears to be desirable. In this study, ~75% of patients refused randomization, perhaps due to the perceived disadvantage of having a 50% chance of a 3-month delay before starting acupuncture treatment. These patients were included in the nonrandomized acupuncture group, which were also followed for 6 months. There were no significant differences with respect to baseline characteristics (with the exception of school education, previous CIM treatment in the last 12 months, AQLQ global score and subscores (''symptoms'' and ''activities'') and treatment outcomes after 3 months between randomized and nonrandomized acupuncture patients. This might be explained largely by the fact that the randomized study was performed in a setting most similar to that of routine care; another setting might have yielded different results. In addition, a results of a systematic review of randomized versus nonrandomized trials could demonstrate, that randomized controlled trials and nonrandomized observational studies could yield similar results.[23] The improvements in the AQLQ score were clinically relevant among both randomized and nonrandomized patients.[18] An additional important finding of this study is that improvements seen immediately after completion of 3 months' treatment continued for the entire 6-month study period. However, the study has not documented any long-term follow-up (e.g., follow-up after 12 months); therefore, this study cannot provide a prognosis of further allergic asthma progression. In addition, some amount of improvement in the acupuncture groups could be due to regression to the mean.

The study is further limited by the fact that without a sham acupuncture group, non-specific (placebo) effects

could not be ascertained. Until now, no published clinical study has investigated the effectiveness of acupuncture in the treatment of bronchial asthma, comparing acupuncture with waiting list controls receiving routine care treatment. Therefore, the results of this study cannot be compared with other clinical trials in which acupuncture was compared to (penetrating or non-penetrating) sham acupuncture or placebo acupuncture. Systematic reviews of acupuncture in the treatment of asthma were inconclusive to address the value of acupuncture in asthma treatment.[11–14] However, it should be noted that the trials reviewed only compared acupuncture with various forms of sham acupuncture. In addition, these trials utilized a maximum study sample of 72 patients; therefore, clinical significance cannot be assumed. Moreover, in most studies, various lung function parameters were the primary outcome measures; in only one was the AQLQ used to assess the primary outcome; however, the assessment was made after only 2 weeks of treatment. Biernacki detected a significant improvement after treatment in the acupuncture and in the sham acupuncture group.[24] A recent trial, published in a internationally well-respected journal, showed that both acupuncture and sham acupuncture had significantly lower effects in an objective outcome measure (Forced Expiratory Volume in 1 Second [$FEV_1$]) when compared to Albuterol, whereas the subjective improvements were the same in all three groups.[25] This indicates that acupuncture might perhaps affect primarily nonspecific factors in patients suffering from allergic asthma.

This study provides further evidence for the safety of acupuncture as an intervention. This conclusion is consistent with findings in large, previously published surveys and trials.[26–28] The finding that the formal qualification of the physician and the years of acupuncture experience had no significant bearing on treatment outcome could be interpreted as a further indication that formal acupuncture training plays only a limited role in the treatment effect. However, these results should be interpreted with caution for two reasons: first, indicators in the present study might not adequately reflect the quality of a physician's treatment and, second, acupuncture may be also administered by non-physician practitioners. In general, our regression analyses identified only one variable (female sex) that predicted treatment outcome.

Since acupuncture is a relatively resource-intensive intervention due to the time involved for both physicians and patients, the question of cost-effectiveness is significant. In earlier research, the cost-effectiveness of acupuncture for certain conditions, such as osteoarthritis of the knee, has been established.[29,30] On the other hand, acupuncture has not been shown to be cost-effective in allergic rhinitis.[31] The recently published cost evaluation of this trial, which included a subgroup of 306 acupuncture patients[32] revealed that costs in the acupuncture group were driven primarily by the acupuncture cost itself. However, because of additional benefits in the acupuncture group, the incremental cost-effectiveness ratio was between €12,810 and €14,911, which many countries view as cost-effective.

To summarize, study results reveal that the use of acupuncture as adjunct to the routine care of allergic bronchial asthma was superior to routine care alone in improving both specific symptoms and general quality of life. Therefore, acupuncture might be considered as a viable option in the treatment of patients with allergic bronchial asthma. High-quality RCT studies that include a sham acupuncture group of sufficient sample size calculation are urgently needed to investigate the specific effects of acupuncture in allergic asthma.

### Availability of Data and Materials

The data can't be shared because it contains data from patients insured with a statutory health insurance and data protection rules only allow use of the data for the aim of the study by the defined cooperation partners.

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### Authors' Contributions

All authors participated in developing the study design and protocol and in revising the manuscript. Specific tasks and responsibilities: general trial coordination (C.M.W., B.B., S.J.); statistical analysis and expertise (S.J., F.L., S.R.); documentation (S.B., K.I.); and overall medical and scientific responsibility (S.N.W.).

### Author Disclosure Statement

No competing financial interests exist.

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Address for correspondence:
*Benno Brinkhaus, MD*
*Institute for Social Medicine, Epidemiology, and Health Economics*
*Charité Universitätsmedizin Berlin*
*Luisenstr. 57*
*Berlin 10098*
*Germany*

*E-mail:* benno.brinkhaus@charite.de