

Title: Non-pharmacological interventions for pollen-induced allergic symptoms: systematic literature review

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ABSTRACT

Background:

Allergic diseases pose a health problem worldwide. Pollen are widespread aeroallergens which can cause symptoms like shortness of breath, cough, itchy eyes or rhinitis. Apart from preventive measures and pharmacological treatment, also non-pharmacological interventions have been suggested to reduce symptoms. The objective of this work was to review studies investigating the effectiveness of non-pharmacologic interventions to reduce allergic symptoms.

Methods:

PubMed, EMBASE and CENTRAL were systematically reviewed in July 2018 and April 2020. Several authors worked on the screening of titles, abstracts and full texts. One author for each literature search performed the data extraction and the Risk of Bias assessment. Studies were included if they met the inclusion criteria defined by the PECO. Studies which investigating the effect of non-pharmacologic interventions on patients with allergic rhinitis were included.

Results:

29 studies investigating eleven types of non-pharmacologic interventions to avoid and reduce allergic symptoms due to pollen exposure were included in this review. Out of all studies, seven studies addressed nasal rinsing and 22 included acupuncture, air filtering, artisanal tears, individual allergen avoidance advice, various nasal applications, self-hypnosis, rhinophototherapy and wraparound sunglasses.

Conclusion:

Most studies had a high Risk of Bias and small sample sizes. There were only a few high-quality studies that give hints about the effectiveness of non-pharmacological interventions. For future research, more high-quality studies are required to confirm the effectiveness of simple, safe and cost-effective interventions.

Key Message:

This paper reviews studies investigating the effectiveness of non-pharmacologic interventions to reduce allergic symptoms due to pollen exposure. The standard treatment of symptoms caused by allergic rhinitis consists of various pharmacological treatments, e.g. immunotherapy, antihistamine or glucocorticoids. Non-pharmacologic interventions show many benefits, as they are easily available, inexpensive and safe to use. In addition, pharmacological interventions may not be effective in helping some patients. We included 29 studies in our analysis and found eleven types of non-pharmacologic interventions to reduce allergic symptoms due to pollen exposure. The following non-pharmacologic interventions were identified: acupuncture, air filtering, artificial tears and cold compresses, individual allergen avoidance advice, nasally applied ointment, nasally applied powder, nasal filters, nasal rinsing, rhinophototherapy, self-hypnosis, wraparound sunglasses. We found indications for the effectiveness of several non-pharmacologic interventions. Due to high risk of bias within the studies, the results should be viewed critically. Further studies are needed to investigate the effectiveness of non-pharmacologic interventions in more detail.

Keywords: allergy, allergic symptoms, non-pharmacological interventions, pollen

Abbreviations:

AR	Allergic Rhinitis
ECHRS	European Community Respiratory Health Survey
ISAAC	International Study of Asthma and Allergies in Childhood
IgE	Immunoglobulin-E
NPI	Non-pharmacologic interventions
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ESM	Electronic Supplementary Material
PROSPERO	International Prospective Register of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
RoB	Risk of Bias
ROBINS-I	Cochranes Risk Of Bias In Non-Randomized Studies
QoL	quality of life
HSNI	hypertonic saline nasal irrigation
VAS	Visual analogue Score

INTRODUCTION

Allergic rhinitis (AR) and asthma pose a worldwide health issue.¹ International studies like the European Community Respiratory Health Survey and the International Study of Asthma and Allergies in Childhood showed that AR and asthma are prevalent in most countries.^{2,3} The global prevalence of AR is between 10% and 30% in adults and at least 40% in children.⁴

AR is associated with an Immunoglobulin-E type antibodies (IgE)-mediated immune response to allergens causing an inflammations. The most common symptoms are rhinorrhea, a blocked nose, nasal itching, sneezing and ocular symptoms.⁵

AR is associated with the development of asthma.^{6,7} Both AR and asthma can be triggered by airborne pollen.⁸ Apart from allergen-specific immunotherapy as the only causal treatment^{9,10}, there is a variety of effective medication and guidelines to control symptoms, e.g. second-generation antihistamine or intranasal glucocorticoids. Bousquet et al.¹¹ showed that symptoms of AR are under control in only about one third of the patients who received optimal pharmacological treatment. The objective of this paper is to review studies on the effectiveness of non-pharmacologic interventions (NPI) to reduce allergic symptoms due to pollen.

METHODS

The 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) checklist has been used to carry out this systematic review (*ESM 1*).^{12,13,14} The review was prepared in accordance with the Cochrane Handbook

for Systematic Reviews of Interventions.¹⁵ The review is registered in the 'International Prospective Register of Systematic Reviews' (PROSPERO: CRD42019106131).

Search strategy

The search strategy was conducted by using PECO's (Table 1 & 2): Studies that investigated the efficacy of NPI in people with allergic symptoms due to pollen were searched. The detailed search strategy is presented in *Table 1*. The date of the search was 18 July 2018. The authors applied a snowball strategy. The snowball strategy is a search strategy in which lists of references are searched for further relevant references. The identified relevant references were screened basing on the inclusion and exclusion criteria. On 17 April 2020, the authors performed an update of the systematic literature search for the period 2018 to 2020 (*Table 1*).

The eligibility criteria were defined on the PECO's and are listed in *Table 2*.

Three researchers built the reviewer team, and screened titles, abstracts and full texts to identify potentially eligible studies. For the update of the literature search, two reviewers screened titles, abstracts and full texts to identify new, potentially eligible studies. The reviewers discussed differences until a common consensus was reached.

Data collection

EndNote X8 was used for data management. Data were extracted onto a data extraction sheet in Microsoft Word 2016. Data was extracted such as author, year, study design, sample size, exposure assessment, comparison, outcome, name of intervention, effect sizes.

Assessment of Risk of Bias (RoB)

The assessment was carried out following the Cochrane Collaboration's tool for assessing RoB in randomized trials.¹⁶ This tool consists of seven domains (Table 3).^{15, 16} The following options for the assessment were used: "low", "unclear" and "high" RoB.^{15, 16}

For non-randomized studies (NRSI), the Cochran's 'Risk Of Bias In Non-Randomized Studies' (ROBINS-I) tool was used to assess the RoB.¹⁷ This tool consists of seven domains (Table 3).¹⁷ The following options for the assessment were used: "low", "moderate", "serious", "critical" RoB and "no information".¹⁷

The factors that were assessed are presented in *Table 3*. The RoB assessment was used to evaluate the internal validity of included studies. Studies with a high or potentially high RoB were not excluded but were presented together with the RoB assessment indicating to ensure a differentiated consideration of the results.

RESULTS

Search results

Results of the systematic literature search are shown in *Figure 1*. Out of 1774 hits, 29 studies could be included in the analysis. Extracted data from all identified studies is presented in *Table 4*. The search identified eleven types of NPI.

RoB assessment

Results of RoB assessment are presented in *Table 3*. The RoB evaluation can be found in the *ESM 2*. Three studies showed a low RoB in the overall assessment. One of the three studies was a NRSI and the other two studies were randomized studies.¹⁸⁻²⁰

Characteristics of included studies

The characteristics of the studies included are shown in *Table 5*. Out of 29 studies, only one study was a NRSI and 28 studies were randomized studies. The studies were published between 2002 and 2020. Sample size varied between $n=4$ to $n=422$ (*Table 5*).

Results of the Interventions

The detailed results of the included studies are presented in *Table 4*.

Three randomized trials^{19, 21, 22} investigated the extent to which *acupuncture* alleviates the symptoms of AR. Brinkhaus et al.²¹ showed, that acupuncture led to increased disease-specific quality of life (QoL) scoring (0.3 point; 95% CI: [0.03, 0.6 point]; $p=0.032$) and a reduction of antihistamine use (1.0 point; 95% CI: [0.2, 1.9 point]; $p=0.018$). However, the clinical significance of these findings is uncertain, because the low effects were within predefined margins. Additionally, the effects did not persist in a follow-up one year later.²¹ Xue et al.²² found effects of acupuncture on nasal ($t=-3.078$, $p=0.003$), other symptoms ($t=-2.206$, $p=0.032$) and the overall severity of SAR symptom ($t=-2.593$, $p=0.012$) but no significant reduction of medication use. In a later study Xue et al.¹⁹ compared effects of real and sham acupuncture groups on rhinitis symptoms for sneezing score (MD= -0.28, 95% CI: [-0.51, -0.05], $p=0.020$), itchiness of ears and palate score (MD=-0.40, 95% CI: [-0.69, -0.11], $p=0.006$) at end of treatment. After four weeks, Xue et al.¹⁹ showed effects of real and sham acupuncture groups on rhinitis symptoms for sneezing score (MD= -0.19, 95% CI: [-0.44, 0.06], $p=0.150$), itchiness of ears and palate score (MD= -0.21, 95% CI: [-0.45, 0.03], $p=0.096$) at end of the follow-up.

Two controlled trials^{23, 24} and one NRSI¹⁸ investigated the effect of *air filters* on symptoms triggered by pollen. The aim of the studies was to reduce the pollen load through air filters. In the NRSI study Bergmann et al.¹⁸ showed that air purifying itself is effective and can prevent allergy symptoms caused by high exposure in a controlled setting (mobile exposure chamber). The exposure in another exposure chamber without air purifier led to the development of nasal symptoms.¹⁸ Brehler et al.²³ tested a filter (Aerovital fresh air ventilators with pollen filters) installation in bedrooms and showed that air filtration can reduce symptoms of hay fever in daily life circumstances. Of 18 patients, 15 (83.3%) reported a decrease in their symptoms when the air filter was active.²³ Li et al.²⁴ investigated the effect of an air purifier (Atmosphere® air purifier (Amway, China)) in bedrooms and showed relative changes of mean differences between the intervention and control groups in symptoms of AR like nasal symptoms (relative change = -0.5, 95% CI: [-1.8, 2.9], $p=0.635$), eye symptoms (relative change = -0.4, 95% CI: [-2.1, 2.8], $p=0.788$) and allergy symptom score (relative change = -3.3, 95% CI: [1.1, 5.5], $p=0.004$).

Bilkhu et al.²⁵ tested in a RCT the efficacy of *artificial tears and cold compresses* on ocular symptoms in an exposure chamber. Both treatments showed an alleviation of acute ocular symptoms in comparison to baseline. The global ocular symptom scores decreased after treatment with cold compresses ($p < 0.001$), artificial tears ($p < 0.001$) and both cold compresses and artificial tears ($p < 0.001$).²⁵ Artificial tears were found to be more effective than cold compresses.²⁵

Three randomized trials²⁶⁻²⁸ analyzed the effects of *advice on individual allergen avoidance*. Bobb et al.²⁶ reported positive associations for individualized pollen avoidance measures, which showed in a reduced wheal size in skin prick test ($r = 0.25$, $p = 0.010$). No significant differences in self-report measures of asthma control were found.²⁶ Smith et al.^{27, 28} conducted two studies with structured allergy history, skin prick testing and appropriate advice on allergy avoidance. The study with adult participants did not observe significant differences between the intervention and control group for any measures of symptoms, QoL or lung function.²⁷ The second study found reduction in symptoms of rhinitis (MD = -3.41, 95% CI: [-6.01, 0.81], $p = 0.010$) and improvement for QoL (MD = -0.50, 95% CI: [-0.68, 0.32], $p = 0.002$) in children.²⁸

Three randomized trials²⁹⁻³¹ analysed *nasally applied ointment*. Geisthoff et al.²⁹ showed in a study with 33 patients that the median of total symptom score for the treatment group decreased from 15.0 at baseline to 9.0 at end of follow-up ($p = 0.0004$). Schwetz et al.³⁰ could reproduce that effect with 106 adult participants ($p = 0.001$) but in addition, the median scores in the placebo group also decreased significantly. However, Schwetz et al found that the preparation was significantly more effective than the placebo.³⁰ Ojeda et al.³¹ reported a small positive effect of a microemulsion on overall nasal symptoms in 110 adults, although this was only statistically significant for nose congestion ($p = 0.011$). No effect was apparent in QoL or patients' satisfaction.

Three controlled trials³²⁻³⁴ investigated a *nasally applied powder* (cellulose). The study by Emberlin et al.³⁴ indicated that the powder reduced medication intake in hay allergy patients ($p = 0.05$). Aberg et al.³² reported a reduction in the total symptom scores from the nose (intervention: M = 7.29; control: M = 6.07; $p = 0.033$) and for running nose (intervention: M = 2.03; control: M = 2.56; $p = 0.017$). The follow-up study³³ showed promising results in decreasing all symptom scores (sneezing, runny nose, blocked nose, eye symptoms, lower airways, sum of nasal symptoms, sum of all symptoms) on a highly significant level (for all $p < 0.001$). As the participants in the active group subjectively perceived the treatment as "good", this result could be clinically significant.

Two randomized trials^{20, 35} described the effects of *nasal filters*. O'Meara et al.³⁵ showed that nasal symptoms, especially sniffles ($p = 0.004$), rhinorrhea ($p = 0.035$) and itchy nose ($p = 0.034$) of patients were reduced after 60 minutes. In Kenney's et al.²⁰ trial, the application of a nose filter significantly reduced the severity of symptoms on a day with high pollen exposure ($p < 0.03$).

Nasal rinsing/irrigation was investigated in seven randomized trials³⁶⁻⁴². Four studies investigated hypertonic saline nasal irrigation (HSNI) in comparison to no treatment and found nasal rinsing to be effective in reducing nasal symptoms and medication intake. Di Berardino et al.⁴¹ found a significant difference for nasal symptoms (intervention: M = 13.60, SD = 10.00; control: M = 29.60, SD = 16.50; $p = 0.01$) and for use of antihistamines (intervention: M = 4.80, SD = 5.20; control: M = 14.80, SD = 14.52; $p = 0.035$). Marchisio et al.⁴⁰ compared HSNI to isotonic saline nasal irrigation (ISNI) solution and found HSNI to be more effective in reducing nasal symptoms like rhinorrhea, nasal itching, sneezing and nasal obstruction (for all $p < 0.0001$). All nasal symptoms improved within four weeks of use. Ischia thermal water was found to be superior to isotonic saline solution. However, a considerable

part of the effect can probably be attributed to the hypertonic properties of the water.⁴⁰ Miraglia et al.³⁶ compared thermal water to isotonic solution. After three month, the group with thermal water had smaller symptom scores than the group with isotonic solution ($p = 0.000023$).³⁶ Xiong et al.⁴² compared tap water to non-tap water and found differences for rhinitis scores in both groups over four weeks (1st week: $p = 0.861$; 2nd week: $p = 0.035$, 3rd week: $p = 0.041$, 4th week: $p = 0.039$).

Alyasin et al.⁴³ investigated the effect of a mixture of ultraviolet A (UV-A), UV-B and visible light irradiated into the nasal cavity (*rhinophototherapy*) in a randomized trial. This study reported a statistically significant impact on all measured symptoms (global severity score and total nasal symptom score) and measured QoL score in the treatment group compared to baseline and placebo groups (for all $p < 0.001$).⁴³

One randomized trial⁴⁴ evaluated the effects of *self-hypnosis*. Langewitz et al.⁴⁴ reported an improvement in scores of the visual analogue Score (VAS) when comparing baseline and follow-up. In the first year, the differences of VAS score between patients who had learned self-hypnosis ($M = -29.2$, 95% CI: $[-38.2, -20.2]$) and the control group ($M = -9.9$, 95% CI: $[-18.0, -1.8]$) were significant ($p = 0.006$).⁴⁴ At the end of the second season, participants of the intervention group showed distinctly lower symptoms ($M = -24.8$, 95% CI: $[-36.8, -12.8]$, $p = 0.60$) and restrictions ($M = -23.7$, 95% CI: $[-36.1, -11.3]$, $p = 0.90$) in comparison to the baseline group.⁴⁴

Two controlled studies^{45, 46} examined the pollen barrier function of *wraparound sunglasses*. Ozturk et al.⁴⁵ showed a statistically significant difference between intervention and control group in ocular symptoms ($p = 0.002$) and antihistamine use ($p = 0.009$). There was no significant difference between intervention and control group in nasal symptoms ($p = 0.256$). Comert et al.⁴⁶ reproduced the results in a slightly larger study group: median IQR changes from baseline in average daily eye itching ($IQR_{Baseline} = -2.26$, $IQR_{Follow-up} = -0.64$, $p < 0.001$), eye watering score ($IQR_{Baseline} = -2.00$, $IQR_{Follow-up} = -1.43$, $p = 0.03$) and TOSS ($IQR_{Baseline} = -3.97$, $IQR_{Follow-up} = -2.40$, $p = 0.002$). The median IQR change in RQLQ scores was higher in intervention group ($IQR_{Baseline} = -1.98$, $IQR_{Follow-up} = -1.10$, $p = 0.02$).⁴⁶ Additionally, there was a statistically significant reduction of sneezing, rhinorrhea and an improvement in QoL.⁴⁶

DISCUSSION

Summary of key findings

This review aims to give an overview over published literature on the effectiveness of NPI to alleviate allergic symptoms. It provides a wide scope while eleven different types of interventions were identified and researched in 29 studies. The RoB analysis showed a low RoB for three studies.¹⁸⁻²⁰ The results should be treated cautiously, because about two thirds of the studies were rated with a high RoB. In this review, significant results and a low RoB assessment were found for acupuncture, air filters/air purifier and nasal filters.

Comparison of NPI results

An effect of *acupuncture* to reduce symptoms was confirmed in three studies^{19, 21, 22} of which one¹⁹ was assessed with a low overall RoB. Xue et al.²² found positive effects regarding the reduction of symptoms. This study had a small sample size (n= 30) and was assessed with a high overall RoB. Brinkhaus et al.²¹ confirms the assumption that belief in acupuncture might influence the results.⁴⁷ While a persistent effect over a period of one year was not significant²¹, another study¹⁹ found positive effects after four treatment-free weeks. In conclusion, there is weak evidence that acupuncture might have a short-term effect in relieving pollen-related symptoms. Future studies with a low RoB are necessary and should identify the conditions (e.g. frequency and duration of treatment), under which acupuncture reduces pollen-induced symptoms.

Three studies investigated the effects of *air filters* in an exposure chamber¹⁸ and in bedrooms^{23, 24}, but two studies cannot provide representative results due to small sample-sizes (n=4¹⁸ and n=44²³). The ROBINS-I tool did not reveal an indication of a high RoB in any category for the study by Bergmann et al.¹⁸ which was the only NRSI trial in this review. Based on the clinical setting, it cannot be concluded that the effect is effective in a normal setting.¹⁸ The studies from Brehler et al.²³ and Li et al.²⁴ did not investigate the pollen concentration in the bedrooms before and after installing the air filter. Thus, statements about the effectiveness of air filters should be viewed critically.^{23, 24} There are various types of filtration systems and sufficient evidence to prove that air filtration reduces indoor levels of ambient particles, which was reviewed by Sublett et al.⁴⁸

One study with a small sample size of 12 participants found *artificial tears and cold compresses* effective in improving ocular symptoms in an exposure chamber.²⁵ Although the presented evidence is small and the RoB was rated as high, the results are in support of existing treatment guidelines.⁴⁹ However, the results should be viewed critically due to a small sample size and a high RoB. But this intervention is an inexpensive, safe and easy option to relieve acute ocular symptoms after high exposure.

The three studies²⁶⁻²⁸ examining the effectiveness of *individual allergen avoidance advice* with over 100 participants each, observed various health outcomes: wheal size in skin prick test²⁶, symptoms, QoL^{27, 28} and lung function²⁷ showing a mixed picture of significant and non-significant results. All three studies²⁶⁻²⁸ were rated with high overall RoB. The effectiveness of individual allergen avoidance advice should be investigated more in future studies.

The impact of *nasally applied ointment* was investigated in three studies²⁹⁻³¹, all of which showed limitations in the RoB assessment. The study of Geithoff et al.²⁹ was rated with a high overall RoB, which may affect the relevance of the results. The results reported by Schwetz et al.³⁰ were consistent with the effects found by Geithoff et al.²⁹ However, in both studies not only pollen as allergens were investigated but also house dust, mites and animal dander were exposure allergens. Schwetz et al.³⁰ was assessed with an unclear overall RoB.

Nasally applied powder was tested in three studies³²⁻³⁴ and can be an option for adjuvant therapy. However, the studies reported mixed results regarding the effectiveness of the measure. The RoB was rated high in Emberlin et al.³⁴

and Aberg et al.³². In the third study³³, uncertainties regarding allocation concealment remain and independent evidence is needed.

The results for the effectiveness of *nasal filters* were positive, but should be interpreted with caution because only two studies^{20, 35} were available, each investigating less than 100 subjects. O'Meara et al.³⁵ was rated as high overall RoB. Overall RoB of Kenney et al.²⁰ was assessed as low, but the authors are patent holders and company shareholders and there is a potential conflict of interest as declared by the authors. Nose filters could be a measure for symptom prophylaxis, but independent studies are needed to prove their clinical efficiency.

For *nasal rinsing/nasal irrigation*, we found the most studies.³⁶⁻⁴² These seven studies show that nasal rinsing is likely to be beneficial and without adverse effects for pollen-induced AR. However, all studies investigating this intervention were rated as high overall RoB. Li et al.⁵⁰ conducted a review and meta-analysis of the efficacy of nasal irrigation in AR. Based on the results, Li et al.⁵⁰ concluded that HSNI is an effective therapy for children with AR, as HSNI lead to a significantly higher improvement of nasal symptoms and reduction in drug intake in comparison with ISNI. These findings show that nasal rinsing/nasal irrigation can be an effective therapy for treating symptoms of AR. Head et al.⁵¹ give an outline for improving future research, e.g. a sufficient trial duration to evaluate the pros and cons of the use of validated measure instruments. Based on the results found in this study, further studies with a low RoB should be conducted.

We identified only one small study⁴³ investigating the effects of *rhinophototherapy*. The results were significant but RoB was rated as probably high. There is a need for further evaluation in clinical trials to confirm the results.

The only study⁴⁴ about *self-hypnosis* reported significant (symptoms at the end of the second season in comparison to baseline; VAS during first season) and non-significant results (symptoms and medication use during first season, nasal flow). However, the overall RoB was assessed as high. Thus, the evidence for the effectiveness of self-hypnosis is very weak.

The effectiveness of *wraparound sunglasses* was researched in two small studies (n= <100)^{45, 46}. Both studies were rated as high overall RoB. This should be considered when evaluating the significant results both studies reported. Wraparound sunglasses could be a convenient and without adverse effects to improve ocular symptoms.

Strength and Limitations

One limitation of our review is the heterogeneity of the included study populations. On the one hand, the study sizes are very different (n=4¹⁸ to n=422²¹), which can distort comparisons of the results. In the included studies different definitions of AR, the severity of symptoms or the use of emergency drugs were used, which limits the comparability of results. For this reason, the comparability of the results is limited.

A strength of this review lies in the broad spectrum of interventions included. There was no predefined list of possible interventions and eleven different NPI could be identified. Furthermore, not only studies with a study population of adults were included, but also studies that examined children^{28, 32, 36-38, 40} or pregnant women³⁹ as test persons.

CONCLUSION

The evidence on the efficacy of NPI to reduce allergic symptoms is low and the included studies are of variable quality. Due to high risk of bias within the studies, the results found should be viewed critically. The authors do not derive any conclusions regarding the efficacy of NPI to reduce allergic symptoms. Some of the identified NPI are effective, easily available, inexpensive and safe to use. Further studies are needed to investigate the effectiveness of NPI in more detail.

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Tables

Table 1: Search term by Database

Data-base	Search term	No. of hits 18.Jul 2018	No. of hits 17.Apr 2020
MED-LINE	(Pollen[tiab] OR allergen[tiab] OR allergens[tiab] OR aeroallergen OR aeroallergens OR "pollen grain" OR "pollen grains") AND (asthma OR "allergic asthma" OR "asthma exacerbation" OR "asthma exacerbations" OR conjunctivitis OR "allergic conjunctivitis" OR "seasonal conjunctivitis" OR rhinoconjunctivitis OR hayfever OR "hay fever" OR pollinosis OR rhinitis OR "seasonal rhinitis" OR "pollen-induced rhinitis" OR "allergic rhinitis" OR "seasonal allergic rhinitis" OR wheeze OR "learning ability" OR "working ability" OR "working capacity") AND ("prevention and control"[sh] OR preventive[tiab] OR prevention[tiab] OR measure[tiab] OR intervention[tiab] OR "avoidance" OR "environmental control" OR "pollen reduction" OR prophylaxis OR adjuvant OR supportive) AND (effective* OR efficacy OR improv* OR "quality of life" OR "life quality" OR "symptom reduction" OR burden OR "symptom management") AND (english[la] OR german [la] OR french[la] OR spanish[la]) NOT immunotherapy NOT animal* NOT dermatitis[tiab] NOT food[tiab] NOT mite*[tiab] NOT fung*[tiab] NOT occupational[tiab] NOT omalizumab[tiab] NOT olopatadine[tiab]	494	37
EM-BASE	(Pollen:ti,ab or allergen:ti,ab or allergens:ti,ab or aeroallergen or aeroallergens or pollen grain*).mp. AND (asthma or allergic asthma or asthma exacerbation or asthma exacerbations or conjunctivitis or allergic conjunctivitis or seasonal conjunctivitis or rhinoconjunctivitis or hayfever or hay fever or pollinosis or rhinitis or seasonal rhinitis or pollen induced rhinitis or allergic rhinitis or seasonal allergic rhinitis or wheeze or learning ability or working ability or working capacity).mp. AND ("prevention and control" or preventive:ti,ab or prevention:ti,ab or measure:ti,ab or intervention:ti,ab or avoidance or environmental control or pollen reduction or prophylaxis or adjuvant or supportive).mp. AND	104	102

	(effective* or efficacy or improv* or quality of life or life quality or symptom reduction or burden or symptom management).mp. AND (english[la] OR german [la] OR french[la] OR spanish[la]) NOT immunotherapy NOT animal* NOT dermatitis:ti,ab NOT food:ti,ab NOT mite*:ti,ab NOT fung*:ti,ab NOT occupational:ti,ab NOT omalizumab:ti,ab NOT olopatadine:ti,ab		
CEN- TRAL	#1: Pollen:ti,ab or allergen:ti,ab or allergens:ti,ab or aeroallergen or aeroallergens or "pollen grain*" #2: asthma or "allergic asthma" or "asthma exacerbation" or "asthma exacerbations" or conjunctivitis or "allergic conjunctivitis" or "seasonal conjunctivitis" or rhinoconjunctivitis or hayfever or "hay fever" or pollinosis or rhinitis or "seasonal rhinitis" or "pollen induced rhinitis" or "allergic rhinitis" or "seasonal allergic rhinitis" or wheeze or "learning ability" or "working ability" or "working capacity" #3: "prevention and control" or preventive:ti,ab or prevention:ti,ab or measure:ti,ab or intervention:ti,ab or avoidance or "environmental control" or "pollen reduction" or prophylaxis or adjuvant or supportive #4: effective* or efficacy or improv* or "quality of life" or "life quality" or "symptom reduction" or burden or "symptom management" #1 and #2 and #3 and #4	709	332

Table 2: Eligibility criteria for included studies

	Study design	PECO			
		Population	Exposure	Comparison	Outcome
Inclusion	Studies describing the effects of symptom-relieving NPI	Children and adults, male and female, sensitized to pollen, confirmed by prick test, IgE test or diagnosis of showing pollen-related allergic symptoms	All kinds of airborne pollen	Baseline, placebo, usual care, no additional treatment	Measures assessing pollen-induced allergic symptoms like AR, allergic asthma, and/or rhinoconjunctivitis, diagnosed or self-reported
Exclusion	Pharmacological studies, study protocols, case studies/series. Studies without an intervention: prognostic, diagnostic, ecological or monitoring studies Basic research studies. (theoretical basic research, animal, cell, genetic, biochemistry and material development studies)	People not sensitized to pollen	Indoor allergens, other allergens than pollen,	No comparator	Other outcomes not showing pollen-induced allergic symptoms
AR = Allergic Rhinitis; IgE = Immunglobulin E; NPI = non-pharmacological intervention					

Table 3: Risk of Bias assessment of included studies

Nb.	Randomized studies	Cochrane Collaboration's tool for assessing risk of bias in randomized trials							
		Random sequence	Allocation concealment	Blinding of participants and	Blinding of outcome	Incomplete outcome data	Selective reporting	Other bias†	Summary assessments
1	Aberg et al. 2011 ³²	+	+	+	+	+	+	-	-
2	Aberg et al. 2014 ³³	+	o	+	+	+	+	+	o
3	Alyasin et al. 2016 ⁴³	o	o	+	-	o	o	+	-
4	Bilkhu et al. 2014 ²⁵	+	o	+	-	+	+	+	-
5	Bobb et al. 2010 ²⁶	+	+	-	-	+	+	+	-
6	Brehler et al. 2003 ²³	+	o	+	+	+	+	+	o
7	Brinkhaus et al. 2013 ²¹	+	+	+	+	+	+	-	-
8	Comert et al. 2016 ⁴⁶	+	o	-	-	+	+	+	-
9	Di Berardino et al. 2017 ⁴¹	+	o	-	o	o	+	+	-
10	Emberlin et al. 2005 ³⁴	+	+	+	+	+	-	+	-
11	Garavello et al. 2003 ³⁸	+	o	-	-	+	+	+	-
12	Garavello et al. 2005 ³⁷	+	o	-	-	+	+	+	-
13	Garavello et al. 2010 ³⁹	+	+	-	-	+	+	+	-
14	Geisthoff et al. 2005 ²⁹	+	o	-	-	+	+	+	-
15	Kenney et al. 2015 ²⁰	+	+	+	+	+	+	+	+
16	Langewitz et al. 2005 ⁴⁴	+	o	-	-	+	+	-	-
17	Li et al. 2020 ²⁴	o	o	+	+	+	+	+	o
18	Marchisio et al. 2012 ⁴⁰	+	o	-	+	+	+	+	-
19	Miraglia et al. 2011 ³⁶	+	o	-	-	+	+	+	-
20	O'Meara et al. 2005 ³⁵	-	+	+	+	o	o	+	-
21	Ojeda et al. 2013 ³¹	+	o	+	+	+	+	+	o
22	Ozturk et al. 2013 ⁴⁵	o	o	-	-	+	+	+	-
23	Schwetz et al. 2004 ³⁰	+	o	o	+	+	+	+	o
24	Smith et al. 2015 ²⁷	+	+	-	-	+	+	+	-
25	Smith et al. 2016 ²⁸	+	o	-	-	+	+	+	-
26	Xue et al. 2002 ²²	+	o	-	-	+	o	+	-
27	Xue et al. 2015 ¹⁹	+	+	+	+	+	+	+	+
28	Xiong et al. 2014 ⁴²	+	o	-	-	+	-	-	-
Nb.	Non-randomized studies	Cochranes Risk Of Bias In Non-Randomized Studies (ROBINS-I)							

		Confounding	Selection of participants	Classification of interventions	Deviations from intended	Missing data	Measurement of outcomes	
29	Bergmann et al. 2016 ^{†8}	+	+	+	+	+	+	+
(+): Low risk of bias; (o): Unclear risk of bias; (-): High risk of bias. † The domain "other bias" includes all possible factors that could influence a possible bias.								

Table 4: Data extraction table

Author (date)	PECO			Intervention	Findings (direct quotes from original study)
	Exposure (Pollen)	Comparison	Outcome		
ACUPUNCTURE					
Brinkhaus et al. 2013 ²¹	Birch and grass	• Baseline • Sham acupuncture plus rescue medication • Rescue medication alone	• Changes in the RQLQ overall score • RMS from baseline • VAS • SF-36 score	• Acupuncture plus rescue medication (cetirizine) • 12 treatments were provided over 8 weeks	• Compared with sham acupuncture and with RM, associated with improvement in RQLQ score: • sham vs. acupuncture mean difference, 0.5 point point; P = 0.001]; • RM vs. acupuncture mean difference, 0.7 point [95% CI, 0.2 to 1.2]; P = 0.001]) • RMS: sham vs. acupuncture mean difference, 1.1 to 1.9 points; P = 0.001]; • RM vs. acupuncture mean difference, 1.5 points [95% CI, 1.0 to 2.0]; P = 0.001]). • Acupuncture led to statistically sig. improvement in QoL and antihistamine use after 8 weeks of treatment compared with sham acupuncture and with RM alone, but the clinical significance of these findings remains uncertain
Xue et al. 2002 ²²	Mixed allergens	sham acupuncture	• Five-point scale of SAR symptom (FPS) • RMS	• Acupuncture • Twelve treatments provided over 4	• Acupuncture sig. improved both nasal (t = −3.078, p = 0.002) and ocular (t = −2.206, p = 0.032) symptom scores, as well as the severity of SAR symptoms (t = −2.593, p = 0.012) • Acupuncture and sham acupuncture group showed no significant difference in SAR symptom scores

				weeks	usage of relief medication.
Xue et al. 2015 ¹⁹	Rye grass	sham acupuncture	• SAR symptom severity • Change of GSS • Change in RQLQ overall score • RMS	• Acupuncture • Twelve treatments provided over 4 weeks	• Acupuncture sig. reduced SAR symptom severity difference=-0.28, 95% CI: -0.51 to -0.05, $F_{1,172} = 0.11$, $F_{1,172} = 7.654$, $p = 0.006$) at the end of treatment • Patient received acupuncture also had sig. better quality of life at 4 weeks follow up after treatment (activity domain: $F_{1,172} = 5.761$, $p = 0.017$) • No sig. difference in weekly total RMS was found at any time point.
AIR FILTER/ AIR PURIFIER					
Bergmann et al. 2017 ¹⁸	Grass	Pollen exposure without filter in the air purifier (sham run)	• TNSS, TOSS and bronchia symptoms (0-12 points) • TNSS (0-3 points in 4 categories)	• Pollen exposure with air purifier: • Exposed twice on two days	• The presence of the air purifier resulted in the control of symptoms in nose, eyes, and bronchia • The level of symptom severity was less than 1 point • The exposure in an exposure chamber in standard conditions with an air purifier led to the development of nasal symptoms of 6 points
Brehler et al. 2003 ²³	Tree and Grass	Placebo filters	• Mean total symptom score (0-3 points in 3 categories) • Peak expiratory flow rates	• Aerovital fresh air filtration systems installed in the bedrooms	• 15 of the 18 (83.3%) patients with only hay fever reported a decrease in their allergy symptoms • When analysing the volunteers' logs, a decrease in symptoms was reported by patients • in the active-filter period and as well, the PEFR was higher in the morning

Bilkhu et al. 2014 ²⁵	Timothy grass	Crossover design, comparison to baseline	• Bulbar conjunctival hyperemia • Ocular surface temperature • GOSS (0-6 points)	• Artificial tears • Cold compresses • Combination of both	• After controlled exposure to grass pollen, CC and ATs had a therapeutic effect on the signs and symptoms of allergic conjunctivitis • GOSS were similar at baseline at each visit ($X = 1.5$), but were significantly lower after treatment (ATs, $X = 0.5$, $P < 0.001$; CC, $X = 0.5$, $P < 0.001$) • The postexposure effect ($X = 2.729$, $P = 0.435$) was not significant • The time after treatment (CC, $X = 88.489$, $P < 0.001$; ATs, $X = 87.639$, $P < 0.001$), with a significant difference between the two groups ($P < 0.001$) • Symptoms more than no treatment ($P < 0.001$), but not significantly different between the two groups ($P = 0.12$)
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			• Repeated before and every 10 minutes after treatment for 1 hour		returned GOSS to baseline levels within 1 hour after treatment. • There was a sig. difference in conjunctival hyperemia between treatments (F = 68.211, P<0.001), with a reduction in hyperemia after treatment (F = 302.764, P<0.001), although this recovery did not differ between treatments (F = 9.469, P<0.001). • There was a sig. difference in temperature after treatment (F = 19.684, P<0.001; Fig 3), with the temperature cooling back to baseline over time (F = 32.955, P<0.001), although this difference differed with treatment (F = 122.796, P<0.001).
INDIVIDUAL ALLERGEN AVOIDANCE ADVICE					
Bobb et al. 2010 ²⁶	Mixed allergens	Usual care	• ACQ • ASES • Lung function measures	• SAI and ATI • IAAA for identified triggers	• At follow-up, patients of the intervention group showed significant associations of their baseline skin prick test wheal sizes with allergens with pollen avoidance measures, r = 0.28.
Smith et al. 2015 ²⁷	Mixed allergens	Usual care	• RQLQ • Asthma QLQ • EQ-5D • RCS and ASS	• Tailored advice in general practice	• No sig. differences were observed between groups for asthma symptoms, quality of life or lung function at 12 months.
Smith et al. 2016 ²⁸	Mixed allergens	Normal care	• RCS and ASS • Pediatric Allergic Disease QoL	• Skin prick testing • Advice on allergy avoidance	• Participants receiving the allergy intervention had significantly fewer asthma symptoms (MD= -3.41, 95% CI= -6.01- 0.81) and significantly better QoL (MD= -0.50, 95% CI=-0.68- 0.32). • There were no sig. changes in asthma symptoms, or no. of days unable to pursue usual activities.

NASALLY APPLIED POWDER					
Aberg et al. 2011 ³²	Grass and Birch	Placebo	• TSS (1-6 points in 5 categories)	• CP • 3 times daily over 4 weeks	• There was a sig. reduction in total symptom score (active 7.29, placebo 6.07, $p = 0.033$) and specifically for itching (active 2.03, placebo 2.56, $p = 0.017$).
Aberg et al. 2014 ³³	Grass	Placebo (lactose powder)	• TSS (1-6 points in 5 categories) • Efficacy score	• CP • Three times daily	• Over the entire 4 weeks, there was a highly sig. reduction in symptoms from the nose, eyes and lower airways compared to the placebo group both for separate symptoms, and all symptoms from upper and lower airways together.
Emberlin et al. 2006 ³⁴	Grass	Placebo (lactose powder)	• Rhinitis nasal symptoms scores (1-5 points in 4 categories) • Medication use • Allergy-related GP visits	• Inert nasal CP	• Some sig. differences were found at the 5% level (nasal symptoms) • No sig. differences occurred between the total Likert scores for the active and placebo groups (Figure 1) (non-parametric test of difference in central tendency) • Very few visits to GPs for allergy related symptoms in either group. • Sig. differences were found in the overall amount of medication taken by the active and placebo groups
NASALLY APPLIED OINTMENTS					
Geisthoff et al. 2005 ²⁹	Mixed allergens	No treatment group	• Mean relative TSS • Mean absolute TSS (0-10 points)	• Lipid-based Nose Ointment	• A sig. change occurred in the symptoms of allergic rhinitis of the test ointment. The median decreased from 5.0 to 2.0 • The mean daily absolute ISS of nasal itching and sneezing was significantly lower in the treatment group • In the treatment group, the mean relative RTSS for itching and sneezing was significantly lower

			in 4 categories)		set decreased by a mean of 38.9 units, with a med
Ojeda et al. 2013 ³¹	Birch, Grass and olive tree	Saline solution	• Mini-RQLQ questionnaire	• Topical micro-emulsion • Twice per day	• The least-squares means for the allergic symptoms patients' diary cards were lower in the active group. • Statistically sig. differences were detected in the nasal congestion ($p = 0.011$), while the difference in nasal symptoms did not reach statistical sig. ($p = 0.05$). • In the per protocol set population, sig. differences were detected in nasal congestion ($p = 0.017$) and mean nasal symptoms.
Schwetz et al. 2004 ³⁰	Mixed allergens	Carboxymethylcellulose gel	• Symptom score (0-6 points) • Nasal air flow	• Pollen blocker cream	• The median score fell from 4 to 1 after application of the cream ($P=0.001$). The median scores in the placebo group were not sig. (ie, from 4 to 3). • The symptom scores demonstrate that the pollen blocker cream had a sig. effect. However, it became apparent that the cream was capable of capturing small quantities of pollen, thus not a true placebo. • Both Alergol and the placebo led to a sig. increase in the rate ($P=0.001$). However, the investigational product was more effective than the placebo.
NASAL FILTER					
Kenney et al. 2015 ²⁰	Grass	Placebo control	• Sum of daily TNSS (0-3 points in 4 categories)	• Nasal Filters for 2 days	• The primary outcome measure of difference in daily TNSS was reduced for the nasal filter when compared with placebo. The median reductions on day 2 of 40% ($P < .02$).

			• Throat irritation • Sum of daily TOSS (0-16 points)		• Difference in maximum TNSS was also sig. reduction in median reductions of 43% on day 2 ($P < .004$) • The difference in TOSS and throat irritation was
O'Meara et al. 2005 ³⁵	Ragweed, Bahia and Bermuda Grass	Placebo	• Self-assessed rhinitis symptoms (Major symptom complex, TSS) • Peak nasal inspiratory flow	• Nasal filter for two hours in a park	• Baseline MSC scores, prior to filter insertion, were similar in the active ($n = 22$) and placebo ($n = 24$) filter groups ($P = 0.02$). • Over the 2-h challenge period MSC decreased in the active group and increased in the placebo group compared with baseline. There were highly significant differences between the groups ($P < .001$). • At 30, 60, 90 and 120 min the net difference in MSC between the groups with placebo filters were -25, -68, -39 and -50% respectively ($P < .001$). • The strongest effect was seen for the symptoms of sneezing ($P = 0.004$), rhinorrhea (overall, $P = 0.035$) and itchy nose ($P = 0.034$), especially at 60 min
NASAL RINSING/NASAL IRRIGATION					
Di Berardino et al. 2017 ⁴¹	Grass	No treatment group	• Saccharine transit time • TNSS and TOSS (0-2 points in 4 or 2 categories) • Medication score	• Hypertonic saline solution in an atomized spray	• In the active group, a sig. decrease of both nasal symptoms and consumption of antihistamines ($p = 0.035$) was observed. • Furthermore, the mucociliary clearance was sig. increased in the control group.
Garavello et al.	Parietaria	No nasal	• Rhinitis score (0-	• Three-times	• Sig. clinical benefits were observed in children with

2003 ³⁸		irrigation	4 points in 4 categories) • Log of oral antihistamine use	daily with hypertonic saline solution	rhinitis to Parietaria who received a regimen of the irrigation with hypertonic saline during the pollen • the mean daily rhinitis score was reduced during treatment period • In regard to the use of oral antihistamines, a reduced drug in patients allocated to nasal irrigation with hypertonic saline was observed
Garavello et al. 2005 ³⁷	Grass	No treatment group	• Rhino-conjunctivitis score (0-3 points in 4 categories) • Intake of oral antihistamines	• Three times daily using the hypertonic saline solution	• Evidence from patients' diary cards showed sig. differences in children who received a regimen of three-times daily hypertonic saline solution • the mean weekly rhinitis score in the active group was lower than the whole pollen period • this difference was statistically sig. in the 6th and 7th weeks • A markedly reduced intake of oral antihistamines was observed in patients allocated to nasal rinsing
Garavello et al. 2010 ³⁹	Parietaria	No treatment group	• Rhinitis score (0-4 in 4 categories) • Antihistamine use • Rhino-manometry	• Intranasal lavage with hypertonic saline solution three times daily	• Evidence from patients' diary cards showed sig. differences in women who received a regimen of 3-times daily hypertonic saline solution during the pollen season • the mean weekly rhinitis score at week 1 was similar to control groups (3.7 ± 1.6 and 4.1 ± 1.9 , respectively) • statistically sig. benefit was documented in all subjects after exposure to Parietaria allergens occurred ($p < 0.001$) • Similar results were observed when focusing on the

					antihistamines.
Marchisio et al. 2012 ⁴⁰	Orchard and rye grass	No treatment group and 0.9% sodium chloride solution group	• TNSS (1-4 points in three categories) • Rhinoscopy • Antihistamine use	• 20-mL of 2.7% (hypertonic) saline solution in • Each nostril, twice a day for four weeks	• Both normal and hypertonic saline sig. lowered the compared with the control group after four weeks the most effective • only in the hypertonic saline group there was a sig. proportion of children with moderate to severe swelling (31.2%, $P < 0.0001$), adenoidal hypertrophy (-30% bilateral OME (-5.0%, $P < 0.0001$)) • Oral antihistamines were used by fewer children in the hypertonic saline group (33/80; 41.2%) than in the isotonic saline group (58/60; 96.7%, $p < 0.0001$) (p=0.34) or the control group (58/60, 96.7%, $p < 0.0001$)
Miraglia et al. 2011 ³⁶	Parietaria	Treatment with 0.9% saline solution(isotonic) solution	• TSS (0-3 points in four categories) • Spirometry • Exhaled nitric oxide	• Crenotherapy with thermal water aerosol for 15 days per month, for three months	• With regard to the rhinitis symptoms, the analysis showed a sig. reduction in the thermal water group of the TSS (mean±SD 206.5±40.3) in comparison to saline solution (mean±SD 316.2±66.2) (Mann-Whitney U test, $p=0.000023$) • Values of FeNO in thermal water group there was a sig. reduction in the mean FeNO levels between T0 and T1 and T2($p < 0.05$) but not between T1 and T2($p = NS$) • The thermal water group had sig. lower FeNO values in group 2 ($p = 0.0001$) • A sig. reduction of the FeNO values was still present two weeks after the end of the therapy

Xiong et al, 2014 ⁴²	Mixed allergens	No additional treatment group	• Symptom score based on QoL questionnaire (0-24 points) • Rhinitis score sum	• Tap water nasal irrigation thrice per day	• There were no sig. differences in rhinitis scores b during the 1st week without any treatment. • There were sig. differences in rhinitis scores betw during the 2nd, 3rd, and 4th week after enrollmen • Tap water nasal irrigation definitely improved all nasal itching, rhinorrhea, nasal obstruction, sneez and impairment of daily activities.
RHINOPHOTOTHERAPY					
Alyasin et al. 2016 ⁴³	Mixed allergens	Comparison to placebo phototherapy with only visible light	• Change in TNSS • GSS • Rhinoconjunctivit is RQLQ	• Visible light, UV-A, and UV-B • 6 treatments over 2 weeks	• Rhinophototherapy sig. improved TNSS score (p and total RQLQ score (p<0.001) compared to plac • The treatment group had sig. less rescue medicati
SELF-HYPNOSIS					
Langewitz et al. 2005 ⁴⁴	Grass and Birch	Usual treatment, Baseline	• Change in nasal flow • Self-reports of symptoms • Use of anti-allergic medication • Change in VAS	• Self-hypnosis was instructed in two to five sessions	• In 39 subjects, the initial pre-study Nasal Provoca compared with the tests performed after induction average relative flow was lower in the initial test performed under self-hypnosis, but none of these statistically sig. • The average diary scores of pollinosis symptoms in year 1 were lower in the intervention group tha this difference did not reach statistical sig. During slight increase in symptoms and restrictions, yet,

Comert et al. 2016 ⁴⁶	Mixed allergens	No treatment group	• RQLQ scores • TNSS (0-6 points in 4 categories) • TOSS (0-6 points in 2 categories)	• Wraparound eyeglasses for three pollen seasons	• Sig. improvements in all symptom and RQLQ scores • Median IQR changes from baseline in average daily symptoms (-1.00 vs -0.64; p<0.001), eye watering score (-2.00 vs -1.37, p=0.002) (-3.97 vs -2.40, p=0.002) • Median IQR change from baseline compared to control group was sig. higher • The median IQR change in RQLQ scores (activities of daily living, ocular symptoms) were sig. higher in sunglass group (-1.98 vs -1.10, p=0.02)
Ozturk et al. 2013 ⁴⁵	region-specific spring-season pollen	No treatment group	• TOSS (1-7 point in 2 categories) • TNSS (1-7 points in 4 categories) • Antihistamine need	• Sunglasses for 3 weeks	• Regarding nasal symptom scores, there was no sig. difference between the 2 groups (p = 0.256) • There was a sig. difference between groups with respect to eye symptoms scores (p = 0.002). • Regarding total symptom scores, there was no sig. difference between the 2 groups (p = 0.245). • Antihistamine need was sig. reduced by wearing sunglasses

Quol 5 dimension scale; FeNO = exhaled nitric oxide; FPS = Five-point scale; GP = general practitioner; GOSS = Global ocular symptom score; GSS = Global symptom score; IAA = Individual allergen avoidance advice; IgE = IgE Immunglobulin E; IQR = Interquartile Range; no. = Number; OME = otitis media with effusion; PFR = peak expiratory flow rates; QoL = quality of life; RAST = Radio-Allergo-Sorbent Test; RCS = Rhinoconjunctivitis score; RMS = Rescue medication score; SAI = Structured Allergy Inventory; SAR = Seasonal allergic rhinitis; sig = significant; SNOT-22 = Sinus Nasal Obstruction and Throat Questionnaire; RTSS = relative total symptom score; SAI = Structured Allergy Inventory; SAR = Seasonal allergic rhinitis; sig = significant; SNOT-22 = Sinus Nasal Obstruction and Throat Questionnaire; TSS = Total symptom score; VAS = Visual analogue scale

Table 5: characteristics of included studies

NPI	Authors	Pollen	Country	Time period	Participant numbers	Age groups (mean age)	Gender (% of females)	S
Acupuncture	Brinkhaus et al. (2013)	Grass, Birch	Germany	2008-2010	422 persons	over 16 (33 years)	male/female (59,5%)	R
	Xue et al. (2002)	Mixed Allergens	Australia	1995	30 persons	over 18 (44.4 years)	male/female (53.3%)	R
	Xue et al. (2015)	Grass	Australia	2009-2011	175 persons	over 18 (42 years)	male/female (58.9%)	R
Air Filters/Air Purifier	Bergmann et al. (2017)	Grass,	Germany	2015	4 persons	over 18 (25-29 years)	male/female (one female)	cr an
	Brehler et al. (2003)	Grass, Tree	Germany	1998	44 persons	over 18 (N.A.)	male/female (23 females)	cr (p
	Li et al. (2020)	Asteraceae	China	2016-2018	90 persons	over 18 (18-65 years)	male/female (55.5%)	R
Artificial Tears and Cold Compresses	Bilkhu et al. (2014)	Grass	UK	N.A.	18 persons	over 18 (29.5)	male/female (12 females)	R
Individual Allergen Avoidance Advice	Bobb et al. (2010)	Mixed Allergens	UK	2005-2006	214 persons	over 18 (47.2 years)	male/female (66.1%)	R
	Smith et al. (2015)	Mixed Allergens	UK	N.A.	278 persons	over 18 (40 years)	male/female (65%)	R
	Smith et al.	Mixed	UK	2010-2011	335 children	between 6 and 16	male/female	R

	(2016)	Allergens				(11.4 years)	(43%)	
Nasally applied powder	Aberg et al. (2011)	Grass, Birch	Sweden	2009	53 children	between 8 and 18 (11 years)	male/female (N.A.)	co p
	Aberg et al. (2014)	Grass	Ukraine	2013	108 persons	over 18 (26.9 years)	male/female (61%)	R
	Emberlin et al. (2006)	Grass	UK	2004	97 persons	over 18 (N.A.)	male/female (57 females)	co p
Nasally applied ointments	Geisthoff et al. (2005)	Mixed Allergens	Germany	2002	33 persons	over 18 (N.A.)	male/female (N.A.)	R
	Ojeda et al. (2013)	Grass, Birch, Tree	Sweden, Spain	N.A.	110 persons	over 18 (34.9 years)	male/female (52 females)	R
	Schwetz et al. (2004)	Mixed Allergens	Germany, Russia	2001	106 persons	over 18 (29 years)	male/female (N.A.)	R cr
Nasal Filter	Kenney et al. (2015)	Mixed Allergens	Denmark	2014	65 persons	over 18 (24.8 years)	male/female (31 females)	R p
	O'Meara et al. (2005)	Grass, Asteraceae	Australia	N/A	48 persons	over 17 (50.6 years)	male/female (29 females)	R
Nasal Rinsing/Nasal Irrigation	Di Berardino et al. (2017)	Grass	Italy	2015	40 persons	over 16 (26 years)	male/female (14 females)	R
	Garavello et al. (2003)	Parietaria	Italy	2001	20 children	between 6 and 12 (N.A.)	male/female (12 females)	no tr
	Garavello et al. (2005)	Grass, Parietaria	Italy	2002	40 children	between 5 and 14 (9.1 years)	male/female (25 females)	R

	Garavello et al. (2010)	Parietaria	Italy	2006-2007	55 pregnant women	over 18 (24 years)	female	R
	Marchisio et al. (2012)	Grass, Orchard	Italy	2010-2011	220 children	between 5 and 9 (80 month)	male/female (38.8%)	R
	Miraglia et al. (2011)	Parietaria	Italy	2009	34 children	between 5 and 14 (9 years)	male/female (20 females)	R
	Xiong et al. (2014)	Mixed Allergens	China	2010-2013	64 persons	over 18 (32 years)	male/female (32 females)	R
Rhinophoto-therapy	Alyasin et al. (2016)	Mixed Allergens	Iran	2014	62 persons	over 18 (36.6 years)	male/female (60%)	R
Self-Hypnosis	Langewitz et al. (2005)	Grass, Birch	Switzerland	2003-2004	79 persons	over 18 (34 years)	male/female (38 females)	R g
Sunglasses	Comert et al. (2016)	Mixed Allergens	Turkey	2011-2013	70 persons	over 18 (28.6 years)	male/female (39 females)	R
	Ozturk et al. (2013)	Mixed Allergens	Turkey	2010	39 persons	over 15 (30.6 years)	male/female (23 females)	C

DB = double-blind; SB = single-blind; RCT = randomized controlled trial

Figures

Fig1 PRISMA flowchart for study selection (adapted from Moher et al.¹³)

Appendices

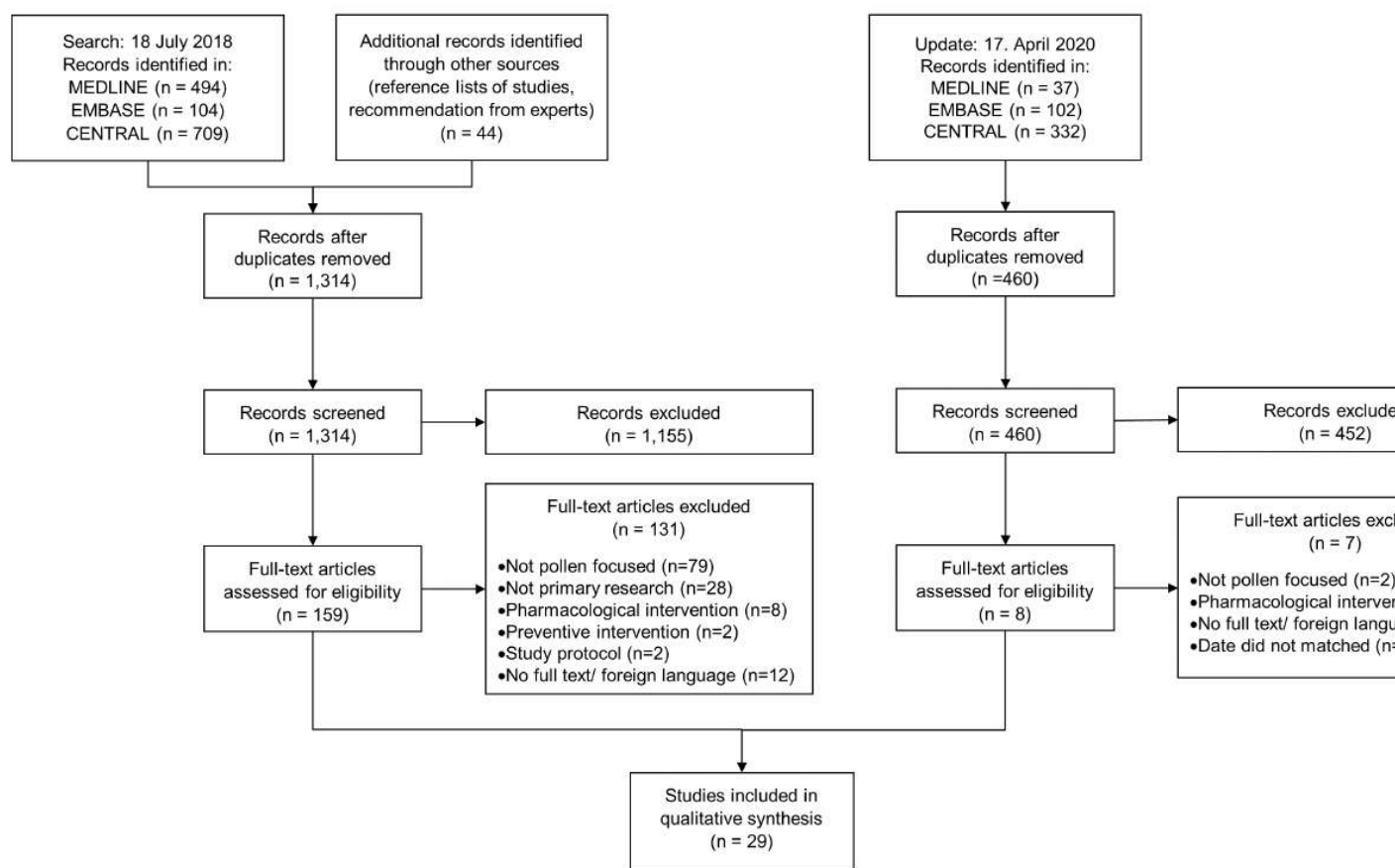
Electronic Supplementary Material 1: PRISMA checklist

Electronic Supplementary Material 2: Risk of Bias Evaluation

Electronic Supplementary Material 3: Instruments of measurement

Figure:**Figure 1** PRISMA flowchart for study selection (adapted from Moher et al. 2009)

This figure was created using program Microsoft PowerPoint 2016



Title: Non-pharmacological interventions for pollen-induced allergic symptoms: systematic literature review

Authors:

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Supplemental Appendix

Electronic Supplementary Material 1: PRISMA checklist

<i>Section/topic</i>	<i>#</i>	<i>Checklist item</i>	<i>Reported on page #</i>
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3 (Table 1)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3 (Table 1)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 (Table 2)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any	3

		processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Table 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3 (Table 3)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<i>RESULTS</i>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4 (Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4 (Table 4 and 5)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	4 (Table 3)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	4-6 (Table 4 and 5)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<i>DISCUSSION</i>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	6

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	6-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
<i>FUNDING</i>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Electronic Supplementary Material 2: Risk of Bias Evaluation

Nb.	Randomized studies	Cochrane Collaboration's tool for assessing risk of bias in randomized trials								Summary assessments	Explanation
		1) Random sequence generation	2) Allocation concealment	3) Blinding of participants and personnel	4) Blinding of outcome assessment	5) Incomplete outcome data	6) Selective reporting	7) Other bias†			
1	Aberg et al. 2011 ¹	+	+	+	+	+	+	-	-	The statistical analysis is too simple. An adequate statistical analysis could have been ANCOVA. The study did not provide any information about a possible conflict of interest.	
2	Aberg et al. 2014 ²	+	o	+	+	+	+	+	o	The study did not provide any information on allocation concealment. Additionally it was complete financed by commercial companies. However the study did not provide any information about a possible conflict of interest.	
3	Alyasin et al. 2016 ³	o	o	+	-	o	o	+	-	The study did not describe or mention a randomization or allocation concealment. There was no blinding of the outcome assessment. Additionally it did not reported loss to follow up or apparent from tables. The study did not provide any information about a possible conflict of interest.	
4	Bilkhu et al. 2014 ⁴	+	o	+	-	+	+	+	-	The study did not provide any information on allocation concealment. No blinding of the outcome was done.	
5	Bobb et al. 2010 ⁵	+	+	-	-	+	+	+	-	No blinding of the participants or personnel was done. The study on individual allergen avoidance advice compared the intervention to usual care as no comparison which could ensure blinding was possible. The study was funded by public foundations.	
6	Brehler et al. 2003 ⁶	+	o	+	+	+	+	+	o	The study did not provide any information on allocation concealment. The study did not provide any information about a possible conflict of interest.	
7	Brinkhaus et al. 2013 ⁷	+	+	+	+	+	+	-	-	Higher beliefs about acupuncture effectiveness was found at baseline in the intervention group, what probably has affected the results. The study was funded by public foundations.	
8	Comert et al. 2016 ⁸	+	o	-	-	+	+	+	-	The study did not provide any information on allocation concealment. There was no blinding of the participants or personnel. The study of wraparound sunglasses only allows a no-treatment comparison. The study did not provide any information about a possible conflict of interest.	
9	Di Berardino et al. 2017 ⁹	+	o	-	o	o	+	+	-	The study did not provide any information on allocation concealment. No blinding of the participants or personnel was done. The outcome were not blinded as there is no adequate placebo intervention available. Additionally it did not reported loss to follow up or apparent from tables.	
10	Emberlin et al. 2005 ¹⁰	+	+	+	+	+	-	+	-	The analyzed data for medication intake are shown in an unclear and inappropriate way. The study was complete financed by commercial companies.	
11	Garavello et al. 2003 ¹¹	+	o	-	-	+	+	+	-	The study did not provide any information on allocation concealment. No blinding of the participants or personnel was done. Outcome were not blinded as there is no adequate placebo intervention available. The study did not provide any information about a possible conflict of interest.	
12	Garavello et al. 2005 ¹²	+	o	-	-	+	+	+	-	The study did not provide any information on allocation concealment. No blinding of the participants or personnel was done. Outcome were not blinded as there is no adequate placebo intervention available. The study did not provide any information about a possible conflict of interest.	
13	Garavello et al. 2010 ¹³	+	+	-	-	+	+	+	-	No blinding of the participants or personnel was done. Outcomes were not blinded as there is no adequate placebo intervention available. The study did not provide any information about a possible conflict of interest.	

Electronic Supplementary Material 3: Instruments of measurement

The following comparators were used. 16 of the included studies compared the intervention to placebo^{1-3, 6, 10, 17-20, 23, 26, 27, 29-31}. Three studies compared to baseline^{4, 16, 30}, one in addition to placebo control, another one in addition to control group with usual care and one in a crossover design under laboratory conditions. 12 studies compared to a no treatment group or a group with usual care as, with exception of one³², the type of intervention does not allow for a comparison to placebo^{5, 8, 11-13, 18, 22, 24, 25, 28, 32, 33}. This is the case for 6 studies of nasal irrigation, with exception of one, which compares different saline concentrations, two studies of wraparound sunglasses and three studies of individual allergen avoidance advice.

The instruments to determine the outcomes found in the studies showed a great variance. All studies applied scoring systems to assess and describe the allergic symptoms, however, the used instruments varied greatly. In six studies, a Total Symptom Score was determined; however, none of the five research teams used the same instrument or scaling^{1, 2, 6, 19, 29, 32}. Three of them used a combination of nasal, ocular and bronchial symptoms^{1, 6, 29}, while the others focused on nasal symptoms^{19, 32}. The Total Nasal Symptom Score was utilized in five studies and consistently evaluated the four symptoms: rhinorrhea, congestion, itching and sneezing as suggested in the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline^{3, 8, 22, 29, 31, 34}. Unfortunately, the severity grading of these differed between studies: 0-3 points^{29, 31, 35}, 0-6 points⁸ or 1-7 points²². The Rhinitis Score used by Garavello et al. is a 0-4-point range variation of the Total Nasal Symptom Score, whereas Di Bernardino uses a 0-2 point scaling for the variables and Geisthoff et al. a 0-10 point scaling for the variables^{11, 13, 32, 33}. One study used a similar score with only three of the symptoms mentioned¹⁸. Di Bernardino et al.'s Ocular Symptom Score, as well as the Total Ocular Symptom Score measure the two symptoms eye watering and eye itching, but with different scales^{8, 12, 22, 33}. Three studies used the Visual Analogue Scale^{16, 17, 30}. O'Meara et al. utilized two different scoring systems: Major Symptom Complex comprised of number of nose blows, number of sneezes, runny nose, sniffles, itchy nose and watery eyes and Total Symptom Complex, comprised of the Major Symptom Complex symptoms plus itchy eyes, itchy ears, itchy throat, cough and postnasal drip²⁰. Seven studies used a score for ocular or rhinitis and asthma symptoms based on the disease-specific quality of life questionnaire^{3, 4, 17, 24, 25, 27, 28}. The study by Li et al. additionally examined the Epworth Sleepiness Score¹⁷.

Only one study investigated asthma⁵, while two assessed a combination of asthma and rhinoconjunctivitis symptoms^{24, 25}. Additionally, 13 studies assessed the change in use of antiallergic medication as a secondary outcome^{6, 10-13, 16, 18, 22, 26, 27, 30, 33}, while six studies assessed the change of health-related quality of life as an additional outcome^{8, 21, 24, 25, 28, 30}. Several studies reported additional clinical outcomes, which were not

considered for the current review: Peak expiratory flow rates^{5, 6}, eosinophil cationic protein level⁶, bulbar conjunctival hyperemia⁴, ocular surface temperature⁴, nasal air flow^{16, 20, 23}, rhinomanometry¹³, rhinoscopy¹⁸ and exhaled nitric oxide¹⁹.

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