The Journal of Laryngology & Otology

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# Role of probiotics in chronic rhinosinusitis: a systematic review of randomised, controlled trials

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**Review Article**

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**Cite this article:** Fong P, Lim K, Gnanam A, Charn T. Role of probiotics in chronic rhinosinusitis: a systematic review of randomised, controlled trials. *J Laryngol Otol* 2023;**137**:1300–1311. https://doi.org/10.1017/S0022215123000543

Received: 8 January 2023
Revised: 26 February 2023
Accepted: 9 March 2023
First published online: 31 March 2023

**Keywords:**
Probiotics; review; rhinitis; sinusitis

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## Abstract

**Objective.** This review evaluated the safety profile and efficacy of probiotics in chronic rhinosinusitis and was registered with Prospero (Centre for Reviews and Dissemination number: 42020193529).

**Method.** Literature databases were searched through inception to August 2022. Randomised, controlled trials exploring adjunctive probiotics in adult chronic rhinosinusitis patients were included. From 948 records screened, 4 randomised, controlled trials were included.

**Results.** Probiotics-associated adverse effects comprised epistaxis and abdominal pain. No reduction in Sino-Nasal Outcome Test values before 4 weeks ($p = 0.58$) or beyond 8 weeks ($p = 0.08$) of treatment or reduction of severe symptom frequency ($p = 0.75$) was observed. Symptom relapse in probiotic-treated patients was significantly lower across all timepoints ($p = 0.045$). Lower sinusitis relapse risks during treatment (risk ratio = 0.49; $p = 0.019$) and 8 months post-treatment (risk ratio = 0.56, $p = 0.013$) were observed. Probiotics demonstrated potential in improving Sino-Nasal Outcome Test symptom subscales, including sleep, psychological and rhinology subscales.

**Conclusion.** The optimal mode of probiotic administration, treatment duration and target patient subgroups requires further study to evaluate the utility of probiotics.

## Introduction

Current guidelines for chronic rhinosinusitis recommend first-line treatment with intranasal steroids or a short course of oral steroids if nasal polyposis is present.[1,2]

Probiotics are defined as non-medicinal substances or supplements that contain live, microbiologically active organisms that are administered with the aim of conferring a health benefit on the patient. In chronic rhinosinusitis treatment, probiotic therapy has been examined as a viable adjunctive treatment following increased understanding of the human–host mucosa microbiome changes in chronic rhinosinusitis, including dysbiosis of the airway microbiome[3] and the link between certain bacterial strains and successful treatment.[4]

Although chronic rhinosinusitis pathogenesis reflects a complex interplay between sinonasal mucosal epithelial barrier dysfunction, immune dysfunction and local microbiome disturbances,[5] probiotic therapy attempts to manipulate and rebalance the alterations in the local microbiome. Postulated mechanisms include propagation of healthy commensals, limiting pathogenic colonisation and biofilm eradication in treating recalcitrant chronic rhinosinusitis.[6,7]

Pre-clinical probiotic therapy models, such as animal models[8] and peripheral blood mononuclear cell challenge models have demonstrated successful probiotic-mediated microbiome manipulation.[9] However, consistent therapeutic effects in chronic rhinosinusitis from probiotics have not been demonstrated clinically.[10] Although probiotic supplementation has immune-modulatory effects on chronic sinus inflammation, its benefits in chronic rhinosinusitis remain undetermined.[11]

This systematic review aimed to critically review all randomised, controlled trials (RCTs) to determine the efficacy of probiotics in chronic rhinosinusitis.

## Materials and methods

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines,[12] with registration in the international database of prospectively registered systematic reviews ('PROSPERO')) in July 2020 (Centre for Reviews and Dissemination number: 42020193529).

### *Literature search strategy*

PubMed, Embase and Cochrane Central Register of Controlled Trials databases were searched from database inception up to August 2022.

Chronic rhinosinusitis was defined to include studies featuring patients with chronic nasal symptoms including nasal obstruction, nasal purulence, hyposmia or anosmia, and facial pain or pressure for a period of at least 12 weeks in the presence of either endoscopic or imaging features compatible with chronic rhinosinusitis, in accordance with European Position Paper on Rhinosinusitis guidelines.[2] Probiotics were defined to include all substances or non-medicinal substances that contained live, microbiologically active organisms administered with the aim of conferring a health benefit on the patient, according to the World Health Organization.[13] The complete search strategy is shown in Figure 1. The references of included studies were hand-searched. All screenings were conducted by two authors independently, and any discrepancies were resolved with a third author.

### Eligibility and selection criteria

Articles published in English were included using the following inclusion criteria: studies with patients aged above 12 years with chronic rhinosinusitis and studies that were RCTs. This review excluded studies with patients who had other concomitant sinonasal conditions such as the following but not limited to: congenital nasal deformities or conditions, sinonasal neoplasms, and previous head and neck radiotherapy.

### Data extraction

The following data were extracted: (1) RCT characteristics including first author, year published, country, study design, trial registration, ethics approval and participant consent; (2) sample characteristics including number of arms, study populations, sample size of recruitment and treatment completion, and age range; (3) intervention characteristics including treatment type, treatment intervention, dosage and duration, treatment provider, control; and (4) outcome characteristics including efficacy evaluated with symptom improvement outcome scores and safety monitored with adverse effects. Corresponding authors were contacted for missing data.

### Outcome measures

In order to assess the change in severity of chronic rhinosinusitis symptoms from baseline to latest follow up, the primary outcome was symptomatic improvement, which was measured with Sino-Nasal Outcome Test (SNOT)-22 or SNOT-20 scores, symptom frequency, relapses and time intervals to relapse. Other outcomes to assess the effects of probiotics included microbiological profiles and inflammatory product changes.

### Risk of bias and quality assessment

Risk of bias of all RCTs was assessed by the Cochrane Risk of Bias Tool for randomised, controlled trials.[14] Results were entered into Review Manager Software (version 5.4.1, The Cochrane Collaboration, 2020).

### Data synthesis and analysis

Symptomatic improvement was recorded as a continuous variable using the SNOT-20 or SNOT-22 symptom score. Standardised mean difference (SMD) was calculated from the mean score reduction, and standard deviations were used for analyses. Standard errors were converted to standard deviations when they were the only values presented. Meta-analysis for SNOT-20 or SNOT-22 symptom scores was performed using Review Manager software and the random effect model. Fisher's exact test was performed for analysis of categorical variables including the incidence of adverse events and side effects of probiotic therapy both within and between studies, using SPSS® statistical software (version 25). Statistical significance was defined with an alpha threshold at 0.05. Other outcomes were qualitatively collected and analysed.

## Results

### Study selection

Our search yielded 1080 records. Three independent reviewers (PF, KL and AG) performed the screening of the article list returned from the initial search. After screening the titles and abstracts, 217 duplicates and 836 irrelevant records were excluded (Figure 1). Twenty-seven potentially relevant studies were further examined, with 23 articles excluded for the following reasons: 10 were not RCTs,[15–24] 2 did not employ probiotics as the intervention for chronic rhinosinusitis,[25,26] 5 did not recruit chronic rhinosinusitis patients as their participants[27–30]1 explored the use of probiotics in paediatric chronic rhinosinusitis patients only,[31] 2 were conference abstracts on self-administered topical probiotics for refractory chronic rhinosinusitis and antimicrobial photodynamic therapy, and 1 was a clinical trial protocol tied to an excluded full text.[32] The remaining four studies were included in our qualitative synthesis,[33–36] 2 of the RCTs were included in our meta-analysis for SNOT-20 or SNOT-22 scores[33,35] and 2 RCTs were evaluated for their incidence of side effects using Fisher's exact tests.[34,35]

### Study characteristics

Four studies[33–36] with a total of 318 chronic rhinosinusitis patients were evaluated in our review (Tables 1 and 2). A total of three parallel RCTs[33,34,36] and one crossover RCT[35] from four different countries were included. Two trials[33,36] included all chronic rhinosinusitis patients, one trial[35] included only chronic rhinosinusitis without nasal polyps patients and one trial[34] included patients with chronic recurrent hypertrophic sinusitis. Most included studies comprised middle-aged adults in Western populations, published within the past two decades. Three RCTs[33,35,36] had a probiotic formulation with bacterial strains belonging to the lactobacillus family, while one[34] had probiotic formulation with bacterial strain belonging to the enterococcus family. Two RCTs[33,36] used oral administration and two[34,35] used the intranasal route. The follow-up duration of these included studies ranged from eight weeks to three months (Table 3).

### Evaluation of methodological quality and bias

Overall, one study had a low risk of bias[33] and three had unclear risk[34–36] (Figures 2a and b). All trials reported dropouts, which ranged from 4.8 per cent to 5.2 per cent.

### Summary of findings

All studies included one or more of the following: safety outcomes, symptom severity score (SNOT-20 or SNOT-22),

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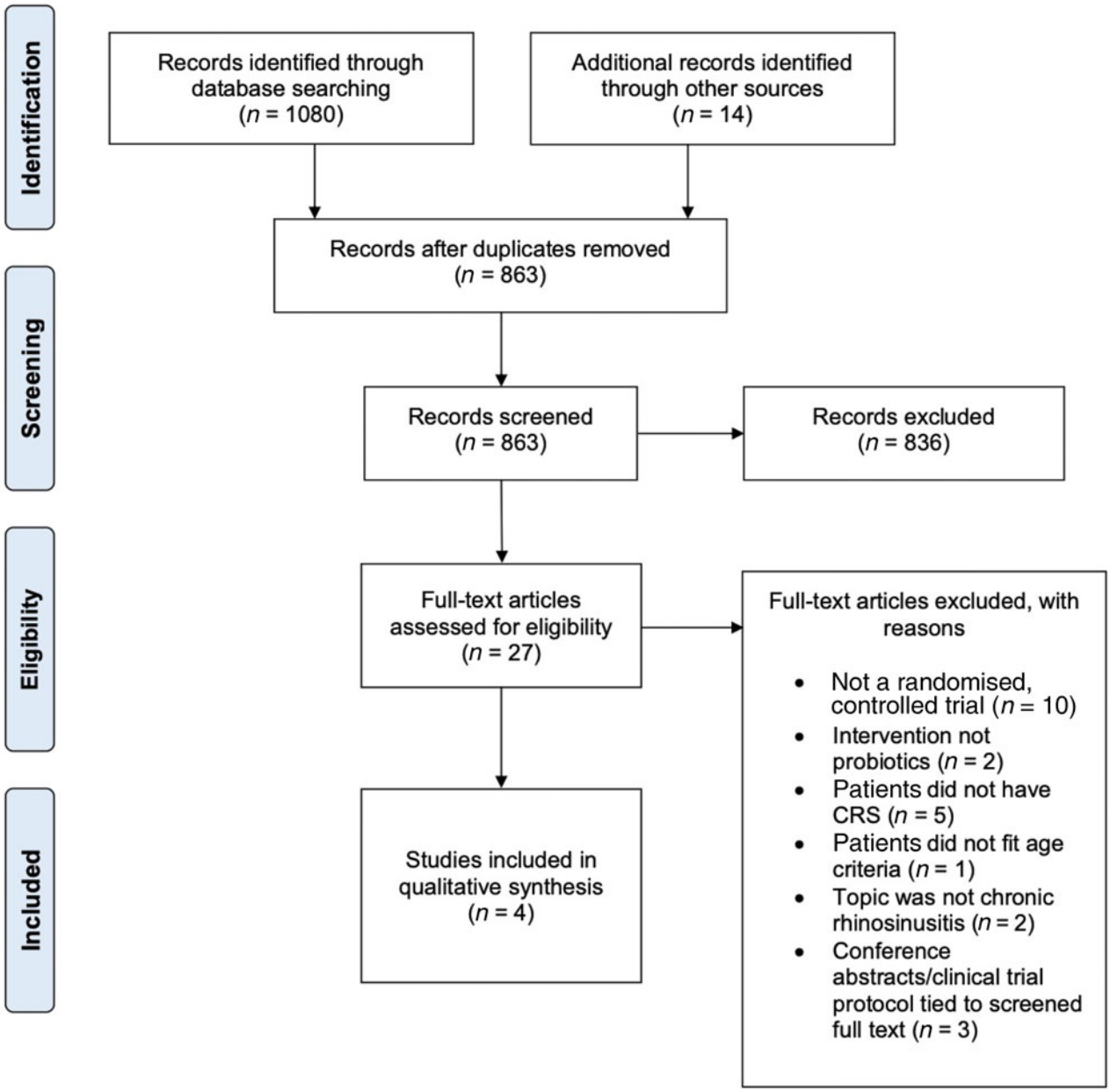


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow diagram of included articles. CRS = chronic rhinosinusitis

temporal score measures of clinical relapses and intranasal endoscopic and microbiological profile changes (Table 3).

### *Safety*

Three out of four studies reported data on safety monitoring,[33–35] whereas one study[36] only reported that the nutraceutical compound was well tolerated in all patients. All included trials only reported minor side effects, where none of the participants withdrew because of side effects. Primary side effects included gastrointestinal symptoms such as nausea and vomiting, abdominal discomfort, and loose stools. A Fisher's exact test was used for analysis of side effect incidence. Within each study, there was no significant difference in side effect incidence when comparing intervention and treatment arms for Mukerji *et al.*[33] ($p = 0.358$), Mårtensson *et al.*[35] ($p = 0.525$) or Habermann *et al.*[34] ($p = 0.854$). We next compared side effect incidence between studies that employed similar probiotic preparations. Mårtensson *et al.*[35] and Habermann *et al.*[34] both utilised nasal probiotic preparations. Incidence of side effects (epistaxis, unpleasant smell or taste) in the intervention arms appeared to be markedly higher in the study by Mårtensson *et al.*[35] compared with Habermann *et al.*[34] (40 per cent *vs* 15.4 per cent, respectively; $p = 0.0148$); however, it should be noted that the sample sizes are markedly different.

Specifically, the incidence of nasal-related side effects in the study by Mårtensson *et al.*[35] was non-significant for epistaxis ($p = 0.548$) and nasal burning sensation ($p = 0.633$) (Table 4). The relative incidence of gastrointestinal side effects between Mårtensson *et al.*[35] (nasal probiotics) and Mukerji *et al.*[33] (oral probiotic) was non-significant ($p = 0.072$).

### *Sino-Nasal Outcome Test scores*

Both Mårtensson *et al.*[35] and Mukerji *et al.*[33] showed that probiotics had no significant difference in mean end-point SNOT-20 or SNOT-22 score reduction for treatment and control groups (Table 5). Probiotic treatment in the study by

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**Table 1.** Summary of included studies' protocol and sample characteristics

| Study | Year | Country | Study type | Trial registration | Arms | Population | Patients (*n*) | Male (*n*) | Female (*n*) | Age (years) | Intervention group | Control group | Ethics approval | Participant consent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mårtensson *et al.*[35] | 2017 | Sweden | Crossover RCT | Nil | 2 | CRSsNP patients | 20/21 | 11 | 10 | 21–80 | 20/21 | 20/21 | 1 | 1 |
| Mukerji *et al.*[33] | 2009 | United States | Parallel RCT | Nil | 2 | CRS patients | 73/77 | 33 | 44 | 15–70 | 38/39 | 35/38 | 1 | 1 |
| Habermann *et al.*[34] | 2002 | Germany | Parallel RCT | Nil | 2 | CRHS patients | 157/157 | 46 | 111 | 18–70 | 78/78 | 79/79 | 1 | 1 |
| La Mantia *et al.*[36] | 2020 | Italy | Parallel RCT | Nil | 2 | CRS patients | 63 | Unstated | Unstated | Unstated (adult patients) | 32 | 31 | 1 | 1 |

RCT = randomised, controlled trial; CRSsNP = chronic rhinosinusitis without nasal polyps; CRS = chronic rhinosinusitis; CRHS = chronic recurrent hypertrophic sinusitis

Mukerji *et al.*[33] showed a significant reduction in SNOT-20 score by 8.1 points ($p = 0.002$) at 4 weeks post-treatment, but it did not sustain significance at 8 weeks ($p = 0.37$). Individual SNOT subscale score domain improvements included sleep (5.5 per cent reduction; $p = 0.02$) and psychological (4.0 per cent reduction; $p = 0.03$) and rhinological subscales (5.0 per cent improvement; $p = 0.03$).

Meta-analysis of pooled SNOT score outcomes showed no reduction in SNOT scores at either timepoint of equal to or less than 4 weeks (standardised mean difference, −0.13; 95 per cent confidence interval (CI), −0.60 to 0.34; $p = 0.58$) (Figure 3a) and at both study endpoints, which were week 8[36] and week 2,[35] respectively (standardised mean difference, −0.33, 95 per cent CI; −0.71 to 0.04; $p = 0.08$) (Figure 3b).

### *Symptom-based outcomes*

The study by Mukerji *et al.*[33] examined patients' self-reported severe symptom frequency. At week 4 of study, a decrease of 33.3 per cent of probiotic-treated and 26.3 per cent of control patients reported severe symptoms. Similarly at week 8, there was no significant difference in reduction of severe symptom frequency in patients when compared with baseline (probiotics 15.3 per cent, control 26.3; $p = 0.75$).

Habermann *et al.* reported a median time to first relapse of 88 days in the probiotic group and 92 days in the control group[34] (Tables 6 and 7). Across all timepoints, there was a significant increase in symptom relapse incidence for control patients compared with probiotic groups ($p = 0.045$). Probiotic-treated patients were also determined to have a significantly lower risk of developing at least one relapse than control-group patients (risk ratio = 0.49; $p = 0.019$) during study periods and the 8-month follow-up period (risk ratio = 0.56; $p = 0.013$).

### *Microbiological profile*

Mårtensson *et al.* examined the microbiological biome changes following probiotic therapy.[35] No significant differences in bacterial composition between observations before and after lactic acid bacteria treatment ($p = 0.219$) or placebo treatment ($p = 0.263$) were observed. Moreover, there were no significant differences in inflammatory cytokine levels (interleukin-6 or 8, interferon-c, tumor necrosis factor-a, myeloperoxidase) within nasal lavage assays following lactic acid bacteria treatment ($p > 0.05$).

## Discussion

Although the definition of chronic rhinosinusitis in our included RCTs varied between studies, all included studies met basic definitions of nasal symptoms for at least 12 weeks, with endoscopic or radiological evidence of chronic rhinosinusitis. We acknowledge that chronic rhinosinusitis is a heterogeneous disease with an evolving spectrum of endotypes. Our review attempted to work with an overall diagnosis of chronic rhinosinusitis, defined broadly to account for heterogeneity in definition across various regions and patient populations. In our review, we opted to include studies of non-paediatric chronic rhinosinusitis populations, with the consideration that adult and paediatric chronic rhinosinusitis may have very different pathophysiology, mandating differing treatment approaches.

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**Table 2.** Main sample characteristics of the study interventions

| First author | Diagnostic criteria | Treatment type | Treatment intervention | Treatment dosage & duration | Treatment provider | Control |
|---|---|---|---|---|---|---|
| Mårtensson *et al.*[35] | EPOS 2012 | Nasal spray | Honeybee lactic acid bacteria | Spray solution contained 5 g of honey & bee pollen & microbiota/10 ml of sterile water; cell count of lactic acid bacteria bioactive metabolites was 1 × 1011 CFU/ml. Each spray contained 100 µl of microbiome from 13 honeybee lactic acid bacteria species (9 lactobacilli species and 4 bifidobacterial species). Instructed to spray two spray doses to each nostril twice daily for two weeks | Self-administration | Placebo (nasal spray) |
| Mukerji *et al.*[33] | University of Miami endoscopic staging system for patients with chronic rhinosinusitis | Chewable tablet | *Lactobacillus Rhamnosus* R0011 | Oral tablet contained probiotic with 500 million active cells of *Lactobacillus Rhamnosus* R0011. Instructed to take the oral tablet twice daily for four weeks | Self-administration | Placebo (tablet) |
| Habermann *et al.*[34] | Clinical established CRHS | Nasal drops | *Enterococcus faecalis* (Group D serological type) | Test preparation contained 1.5–4.5 × 107 per milliliter of *Enterococcus faecalis* bacteria of serological group D with cells and autosylate. Instructed to take 30 drops of active drug thrice daily for 26 weeks (6 months) | Unstated | Placebo (starch suspension diluted in isotonic saline solution) |
| La Mantia *et al.*[36] | Unstated | Oral nutraceutical 'stick' | Abincol® containing *Lactobacillus plantarum* LP01, *Lactobacillus lactis* subspecies cremoris LLC02 & *Lactobacillus delbrueckii* LDD01 (concurrent oral antibiotic tablets for 7–10 days) | Test preparation contained *Lactobacillus plantarum* LP01 (1 billion living cells), *Lactobacillus lactis* subspecies cremoris LLC02 (800 million living cells) and *Lactobacillus delbrueckii* LDD01 (200 million living cells). Instructed to take 1 stick daily for 4 weeks straight together with the antibiotics | Self-administration | Unstated |

EPOS = European Position Paper on Rhinosinusitis; LAB = lactic acid bacteria; nasal polyps CFU = colony forming unit; CRHS = chronic recurrent hypertrophic sinusitis

**Table 3.** Summary of results of the included studies

| First author | Parameters collected | Duration of follow-up | Results | Drop out |
|---|---|---|---|---|
| Mårtensson *et al.*[35] | SNOT-22, immunological markers, number of patients with specific bacterial species | 8 weeks: 2 weeks intervention, ≥4 weeks washout, 2 weeks sham | No statistically significant change in symptoms scores was recorded | 1/21 (no reason given) |
| Mukerji *et al.*[33] | SNOT-20, symptom frequency score | 8 weeks: 4 weeks intervention, 4 weeks follow up | Improved: SNOT-20 scores in both placebo & treatment group at week 4 ($p = 0.02$ for placebo and $p = 0.002$ for treatment) but not at 8 weeks. No changes in symptom frequency. No significant differences between treatment group & placebo | 1/39 in intervention group (no reason given, dropped out after baseline measurement) 3/38 in placebo group (no reason given, dropped out after baseline measurement) |
| Habermann *et al.*[34] | Number of patients who experienced 2 or more relapses. Number of patients who experienced at least 1 relapse. Number of patients who experienced relapse | 14 months: 6-month intervention, 8-month follow up | Improved: reduced relative risk of at least 1 relapse of sinusitis in treatment group compared with placebo ($p = 0.019$ during treatment period & $p = 0.013$ during follow up) & frequency of relapses in treatment group compared with placebo ($p = 0.045$). Treatment group had significantly greater improvement than placebo | 0 |
| La Mantia *et al.*[36] | Percentage of difference in number of participants between intervention & control groups reporting symptoms evaluated (fever, tiredness, headache, pain, malaise, diarrhoea, urinary tract infection, nausea) at timepoint 1 with antibiotic therapy (7–10 days), timepoint 2 at the end of a 4-week probiotics course (1 month) and timepoint 3 at 3-month follow up (90 days) | 3 months | Improved: probiotic mixture reduced the intensity of symptoms during time 1, time 2 and time 3 more than control. Probiotic mixture also reduced the frequency of clinical relapse & additional medications needed to a larger extent than control. Probiotic group experienced less tiredness, headache, pain and malaise than control at time 1 (7–10 days) ($p < 0.001$ for all symptoms) | Unspecified |

The following species of bacteria were utilised the study: *Lactobacillus apinorum Fhon13N, Lactobacillus mellifer Bin4N, Lactobacillus mellis Hon2N, Lactobacillus kimbladii Hma2N, Lactobacillus melliventris Hma8N, Lactobacillus helsingborgensis Bma5N, Lactobacillus kullabergensis Biut2N, Lactobacillus kunkeei Fhon2N, Lactobacillus apis Hma11N + Bifidobacterium asteroides Bin2N, Bifidobacterium coryneforme Bma6N, Bifidobacterium Bin7N and Bifidobacterium Hma3N. SNOT = Sino-Nasal Outcome Test

Our review showed that probiotics are safe for clinical use, with extremely low adverse event risks. The most common side effects were gastrointestinal in nature. The systemic side effects of probiotics were interesting as there was no direct systemic absorption of probiotics into the gastrointestinal tract for 2 of 3 studies that used nasal probiotic preparations, yet gastrointestinal symptoms were the predominant side effects. We note the non-significant difference in relative incidence of gastrointestinal side effects between Mårtensson *et al.*[35] (nasal probiotics) and Mukerji *et al.*[33] (oral probiotics). The study by La Mantia *et al.*[36] did not report any gastrointestinal side effects with the use of an intranasal probiotic nutraceutical 'stick', despite concurrent use of antibiotic treatment for 7–10 days, which may affect the gut microbiome. Although these studies were unable to ensure that dietary intake of the study participants did not contain any probiotic-containing foods during the study period, we acknowledge gastrointestinal side effects remain prevalent regardless of probiotic delivery method, and this requires further studying. Current trials examining the effect of ingested oral probiotics with respect to alterations in both nasal and intestinal microbiomes are under way.[37] Early studies report alterations in nasal microbiomes following oral probiotic treatment, but have yet to establish if the reverse is true.[38] Similar to intranasal steroids, which are a mainstay of medical chronic rhinosinusitis treatment because of excellent safety profiles,[39] the systemic side effect profile of probiotics should be determined if intended for application as chronic rhinosinusitis adjunctive treatment.

We attempted to evaluate study outcomes by directly comparing the included studies with the subtypes of probiotic preparation used. However, this proved untenable because of the small number of included studies, heterogeneity of study outcomes with little overlap and significant variation in reporting of outcomes.

Our review also examined pre- and post-study changes in validated symptom scores, such as SNOT scores. Overall, a meta-analysis of pooled data illustrates that there was no significant reduction in SNOT scores at either timepoint of less than four weeks or at both study endpoints at eight weeks and two weeks. Although both studies reported no significant reduction in SNOT scores, we performed a pooled analysis to factor in the effect size of each RCT and to quantify the absolute decrease in mean SNOT scores, which ranged from a maximum of 6.5 to 8 points at initial stages. This does not consistently meet the minimum clinically important difference for SNOT-22 scores of 8 points (for medical therapy) or 9 points (for endoscopic sinus surgery) as established in the current literature, where minimum clinically important difference is defined as the minimum change in an objective clinical outcome value following a clinical intervention that is associated with a clinically detectable change for the patient.[40] This suggests that from a patient symptom perspective, overall

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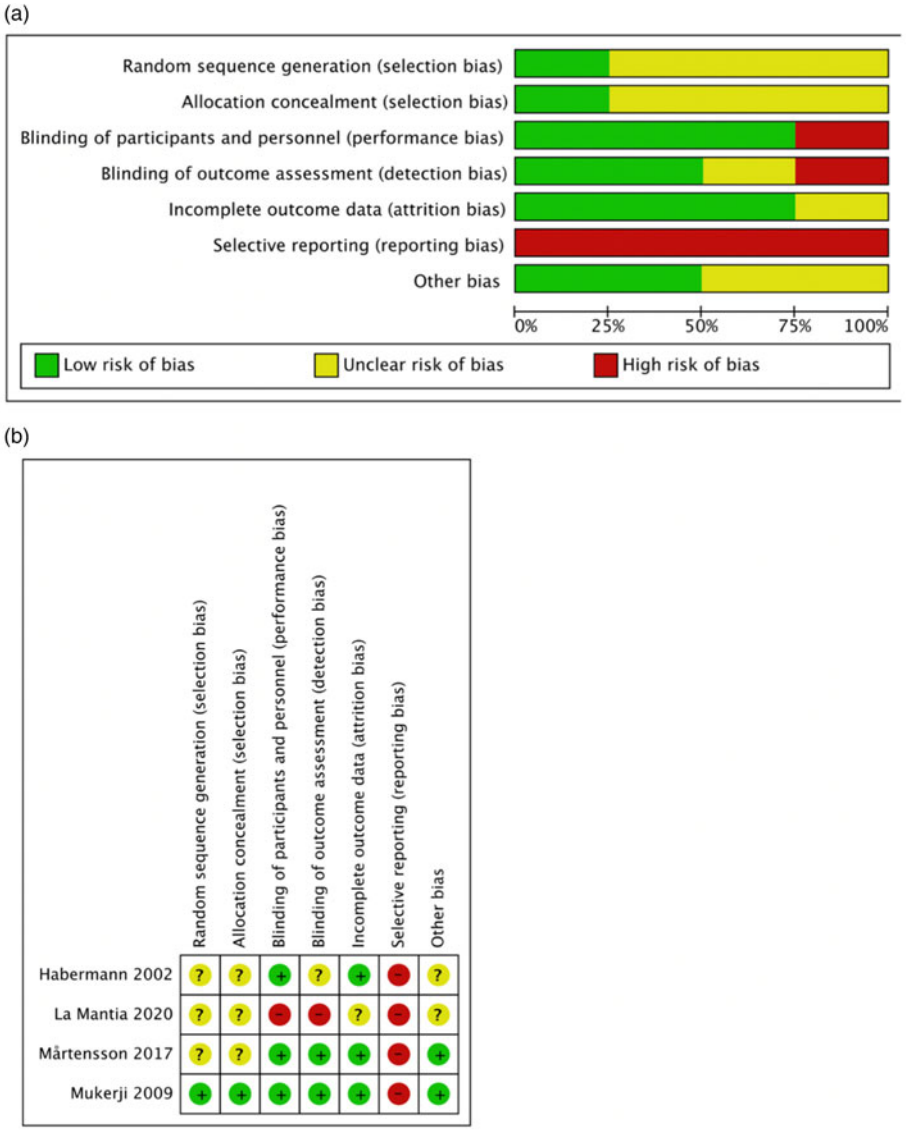


**Figure 2.** (a) Risk of bias graph. (b) Risk of bias summary.

symptom reduction may be marginal or insignificant with probiotic use. However, SNOT subscale breakdown analysis showed significant improvements in the sleep (5.5 per cent reduction; $p = 0.02$) and psychological (4.0 per cent reduction; $p = 0.03$) and rhinological subscales (5.0 per cent improvement; $p = 0.03$).[33] Although overall sleep and psychological effects may be multifactorial, probiotics may be effective in improving nasal symptoms. The actual percentage decrease of 5 per cent in these subscores may appear minimal but may illustrate a trend towards improvement with consistent probiotic use. As chief symptoms in chronic rhinosinusitis tend to be rhinological, a considerable proportion of chronic rhinosinusitis patients may derive symptom improvement following probiotic use. An alternate study by La Mantia *et al.*[36] affirmed that probiotic use significantly reduced intensity of sinusitis symptoms (tiredness, headache, pain, malaise) in both acute and chronic rhinosinusitis patients. Together, these findings suggest promising symptom-control efficacy of probiotics in chronic rhinosinusitis.

Our review attempted to ascertain the optimal regime and application of probiotics for chronic rhinosinusitis. Mukerji *et al.*[33] showed a significant reduction in SNOT-20 score of 8.1 points ( $p = 0.002$) at 4 weeks post-treatment, but this treatment effect did not sustain significance at 8 weeks ( $p = 0.37$). This suggests an optimal period for duration of therapy (i.e. between four and eight weeks) as there may be a rebound phenomenon in prolonged probiotic therapy beyond eight weeks. Further studies are warranted to determine whether local mucosal changes following prolonged treatment bears resemblance to the clinical entity of rhinitis medicamentosa following prolonged nasal decongestant therapy. The probiotic formulation in the study by Mukerji *et al.*[33] used single-strain probiotics, whereas in the study by Mårtensson *et al.*[35] they employed a composite formulation (13 species of honeybee lactic acid bacteria). Current understanding of probiotics' therapeutic effect suggests that probiotic multi-species formulas may be more effective against a wide range of endpoints when compared with single species formulas.[41] More studies are required to determine the optimal probiotic composition for adjunctive use in chronic rhinosinusitis.

The findings from Mukerji *et al.*[33] of decreasing severe symptom frequency rate for the probiotic intervention group from 33.3 per cent at week 4 to 15.3 per cent at week 8 highlights the effect of probiotic therapy in reducing symptom severity. Because the efficacy of probiotics in symptom reduction appears to taper off towards eight weeks of treatment, an optimal treatment duration of adjunct probiotic therapy may be between 4 and 6 weeks.

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**Table 4.** Summary of the adverse effects profile of the included studies

| First author | Adverse effects in intervention | | Patients who dropped out due to adverse effects (intervention) (*n*) | Adverse effects in control | | Patients who dropped out due to adverse effects (control) | *P*-value of withdrawal rate (between intervention & control) | *P*-value of withdrawal rate (between intervention & control) |
|---|---|---|---|---|---|---|---|---|
| **Mårtensson *et al.*** [35] | Intervention only (crossover design) | Burning sensation in nose (*n* = 1). Coughing (*n* = 1). Unpleasant smell (*n* = 1) | 0 | Sham only (crossover design) | Stomach problems (*n* = 3). Coughing (*n* = 1). Minor nose bleed (*n* = 1) | 0 | Unstated | Unstated |
| | Intervention & sham (crossover design) | Burning sensation in nose (*n* = 2). Diffuse stomach problems (*n* = 1). Coughing (*n* = 1). Minor nose bleed (*n* = 1) | | Sham & intervention (crossover design) | Burning sensation in nose (*n* = 2). Diffuse stomach problems (*n* = 1). Coughing (*n* = 1). Minor nose bleed (*n* = 1) | | | |
| | Intervention total (crossover design) | Burning sensation in nose (*n* = 3). Coughing (*n* = 2). Unpleasant smell (*n* = 1). Diffuse stomach problems (*n* = 1). Minor nose bleed (*n* = 1) | | Sham total (crossover design) | Burning sensation in nose (*n* = 2). Diffuse stomach problems (*n* = 4). Coughing (*n* = 2). Minor nose bleed (*n* = 2) | | | |
| Mukerji *et al.*[33] | Bloating (*n* = 7; 18.4%). Diarrhoea (*n* = 8; 21.1%). Abdominal pain (*n* = 7; 18.4%). Loose stools (*n* = 9; 23.7%). Total number of patients with adverse effects reported (*n* = 14; 36.8%) | | 0 | Bloating (*n* = 9; 25.7%). Diarrhoea (*n* = 10; 28.6%). Abdominal pain (*n* = 7; 20.0%). Loose stools (*n* = 8; 22.9%). Total number of patients with adverse effects reported (*n* = 17; 48.6%) | | 0 | Unstated | 0.31 (any gastrointestinal side effect), 0.45 (bloating), 0.46 (diarrhoea), 0.86 (abdominal pain), 0.93 (loose stools) |
| Habermann *et al.*[34] | Disgust, nausea, vomiting, nasty taste of the study medications, meteorism (*n* = 12) | | 0 | Disgust, nausea, vomiting, nasty taste of the study medications, meteorism (*n* = 13) | | 0 | Unstated | Unstated |
| La Mantia *et al.*[36] | Unspecified. Nutraceutical compound was well tolerated in all patients | | | | | | | |

**Table 5.** Summary of SNOT scoring outcomes for included studies

| First author | SNOT-20 outcomes used | Timepoint | Mean score reduction (intervention) | Standard deviation (intervention) | *P*-value (intervention) | Mean score reduction (control) | Standard deviation (control) | *P*-value (control) | *P*-value (control & intervention) | *P*-value (time averaged changes in SNOT-20 from baseline) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mårtensson *et al.*[35] | SNOT-22 | Week 2 | Median baseline: 45.5 (IQR, 23.0–58.5). Median after LAB: 38.0 (IQR, 28.0–68.5) | Unstated | 0.862 | Median baseline: 45.5 (IQR, 23.0–58.5). Median after sham: 34.0 (IQR, 17–55) | Unstated | 0.577 | 0.082 | Unstated |
| | SNOT-22 rhinological domain | Week 2 | Median baseline: 18.0 (IQR, 12.5–24.0). Median after LAB: 19.0 (IQR, 15–28.5) | Unstated | 0.471 | Median baseline: 18.0 (IQR, 12.5–24.0). Median after sham: 17.5 (IQR, 9.0–23) | Unstated | 0.992 | 0.061 | Unstated |
| Mukerji *et al.*[33] | SNOT-20 | Week 4 | 8.1 | 14.7 | 0.002 | 7.1 | 16.6 | 0.02 | 0.79 | 0.98 |
| | | Week 8 | 1.8 | 12.0 | 0.37 | 5.5 | 14.0 | 0.02 | 0.23 | |
| | SNOT-20 specific domains | Week 4 | Improvement from baselines total (placebo & probiotics). | Unstated | Unstated | Improvement from baselines total (placebo & probiotics). | Unstated | Unstated | Unstated | Unstated |
| | | Week 8 | | Unstated | Unstated | | Unstated | Unstated | Unstated | Unstated |
| | | | Ear & facial subscales: improved by 3.6% ($p = 0.08$). Sleep subscale: improved by 5.5% ($p = 0.02$). | | | Ear & facial subscales: improved by 3.6% ($p = 0.08$). Sleep subscale: improved by 5.5% ($p = 0.02$). | | | | |
| | | | Psychological subscale: improved by 4.0% ($p = 0.03$). | | | Psychological subscale: improved by 4.0% ($p = 0.03$). | | | | |
| | | | Rhinological subscale: improved by 5.0% ($p = 0.03$) | | | Rhinological subscale: improved by 5.0% ($p = 0.03$) | | | | |

SNOT = Sino-Nasal Outcome Test; IQR = interquartile range; LAB = lactic acid bacteria

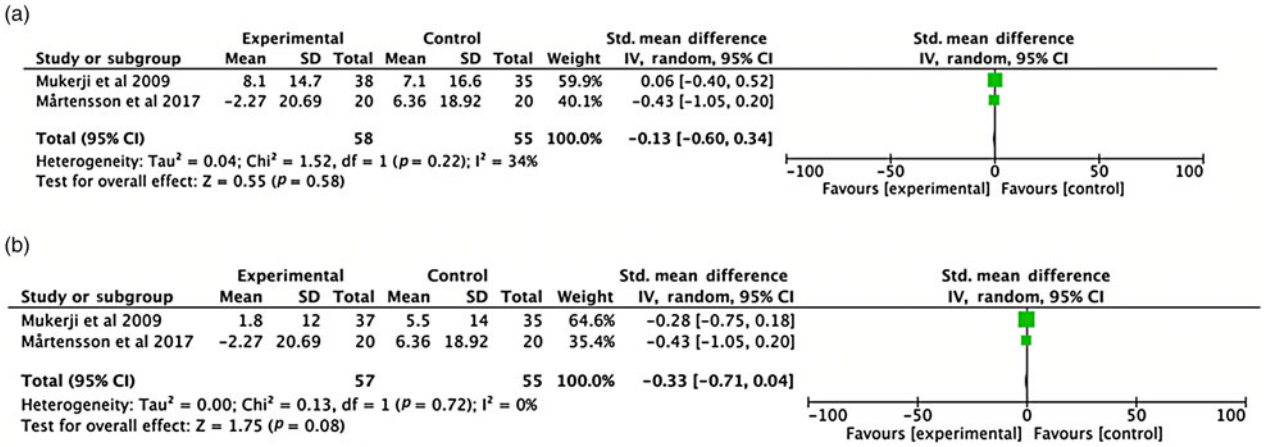


**Figure 3.** (a) Effects of probiotics on SNOT outcomes at timepoint less than or equal to 4 weeks. (b) Effects of probiotics on SNOT outcomes at experimental end-points. Std. = standardised; SD = standard deviation; CI = confidence interval; IV = inverse variance

**Table 6.** Summary of included studies' relapse outcomes

| | | Number of patients who experienced 2 or more relapses (*n* = patients/month) | | Number of patients who experienced at least 1 relapse (*n* = patients/month) | | Number of patients who experienced relapse (*n* = patients/month) | | |
|---|---|---|---|---|---|---|---|---|
| First author | Time point | Number of patients (intervention) | Number of patients (control) | Number of patients (intervention) | Number of patients (control) | Number of patients (intervention) | Number of patients (control) | *P*-value |
| Habermann *et al.*[34] | Week 24 | 1 | 8 | 15 | 15 | 17 | 33 | 0.045 |
| | Week 56 | Unstated | Unstated | 24 | 30 | 33 | 57 | 0.045 |

**Table 7.** Summary of included studies' relapse outcomes

| | Median time span from the beginning of the study to the second relapse | | | Median time span from the beginning of the study to the first relapse | |
|---|---|---|---|---|---|
| First author | Number of patients (intervention) | Number of patients (control) | *P*-value | Number of patients (intervention) | Number of patients (control) |
| Habermann *et al.*[34] | 703 | 413 | 0.03 | 513 | 311 |

Finally, we explored alternative clinical contexts for adjunctive probiotic use. Habermann *et al.*[34] reported that the relative risk of sinusitis relapse was much lower in probiotic treatment groups compared with their control counterparts (risk ratio = 0.49; $p = 0.019$) during the study period and the 8-month follow-up period (risk ratio = 0.56; $p = 0.013$). Similarly, La Mantia *et al.*[36] reported that probiotic treatment reduced episodes of chronic rhinosinusitis relapse by between 31 and 45 per cent within 1 month and up to 20 per cent within 3 months. These studies suggest that probiotics may have a key role in minimising the risks of acute chronic rhinosinusitis episodes.

## Strengths and limitations

Firstly, very few previous studies have summarised the evidence for probiotics in chronic rhinosinusitis, where only *in vitro* potential has been demonstrated, but clinical benefits are yet to be explored.[3,11,42] This study is the first review to comprehensively assess the efficacy of probiotics in all RCTs evaluating probiotics in chronic rhinosinusitis and provide updated recommendations for future trial designs. Secondly, this review is also the first to holistically evaluate both the safety profile and clinical effectiveness demonstrated by SNOT, symptom-based outcomes and microbiological profile across all RCTs.

However, this review is limited by the small number of RCTs exploring probiotic treatment in chronic rhinosinusitis, which affects consequent stratification to explore variation in response to probiotics among different patient profiles. These include stratification by age, gender and disease characteristics including nasal polyp percentage and duration of prior medical treatment for chronic rhinosinusitis. Moreover, there is heterogeneity in modes of probiotic administration and outcome measures. Ideally, the studies that administered oral probiotics should be separately analysed from studies that utilised non-oral probiotic formulations (e.g. nutraceutical nasal stick). Furthermore, studies could have been analysed based on species of probiotic bacteria (e.g. lactobacillus *vs* enterococcus). However, the extremely small number of included RCTs rendered the above stratification unfeasible. As such, our study aimed to pool the available evidence on probiotic use to evaluate the utility of probiotics in chronic rhinosinusitis treatment. Further studies investigating nasal probiotics as an adjunct treatment for chronic rhinosinusitis are awaited. Standardised reporting outcomes using validated rhinological and symptom scores are recommended for future RCTs.

https://doi.org/10.1017/S0022215123000543 Published online by Cambridge University Press

Besides utility as an adjunctive therapy for chronic rhinosinusitis patients on maximal medical therapy, the role of probiotics in high-risk patient groups can be potentially examined. These include recurrent sinusitis subgroups (more than four sinusitis episodes with intervening symptom-free periods) or in post-operative endoscopic sinus surgery patients in whom risks of acute sinusitis may compromise surgical outcomes. We further observed the complex interplay of commensal and pathogenic bacteria in the sinonasal microbiome. Cho *et al.*[43] demonstrated via *in vitro* study that the effect of single-strain intranasal probiotics can have vastly differing growth effects on pathogenic bacteria. Intranasal application of a probiotic rinse containing *Lactococcus lactis* suppressed growth of *Pseudomonas aeruginosa* in one strain but induced growth in a mucoid strain. In contrast, Endam *et al.*[21] demonstrated that intranasal probiotic irrigation with live *L. lactis* W136 bacteria in patients with refractory chronic rhinosinusitis was safe. This was further associated with beneficial effects on symptoms, mucosal aspect and microbiome composition. Within our included studies, Mårtensson *et al.*[35] did not report any significant difference in the concentration of pathogenic bacteria species or inflammatory cytokine levels, although it is relevant to note that probiotic therapy (lactic acid bacteria) administered using the study dose of 108 CFU of lactic acid bacteria to each nose twice daily did not exert any bacterial or inflammatory process interference. These must be factored into devising adjunctive probiotic therapy regimes for chronic rhinosinusitis.

## Conclusion

Probiotic therapy does not exert significant adverse events as adjunctive treatment in chronic rhinosinusitis and shows efficacy in improving primarily rhinological symptoms. This review calls for future RCTs to explore optimal treatment duration and bio-absorption of intranasal topical probiotics and their effects on high-risk sinusitis patient subgroups to fully determine the utility of probiotics in chronic rhinosinusitis.

**Acknowledgements.** We would like to thank Ms Hui Cheng, senior statistician in Clinical Governance, Sengkang General Hospital, for her input and consult regarding statistical design and direction for this study.

**Competing interests.** None declared

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