Preventing Respiratory Tract Infections by Synbiotic Interventions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Dysbiosis of the human gut microbiome has been linked to various health conditions, including respiratory tract infections (RTIs) through the gut–lung axis. Several trials have reported that synbiotic therapy could help prevent RTIs or relieve symptoms of some diseases. This meta-analysis comprehensively evaluates the clinical effects of synbiotic supplements for preventing RTIs. PubMed and Google Scholar were searched by keywords for eligible clinical trials until April 2019. Sixty-two studies were retrieved, and 16 studies were selected for meta-analysis. The primary outcomes were defined as the proportion of participants with RTIs at least once or the times of RTI episodes during follow-up based on the intention-to-treat approach. Overall, synbiotic interventions reduced the incidence rate of RTIs by 16% (95% CI: 4%, 27%) and the proportion of participants experiencing RTIs by 16% (95% CI: 5%, 26%). There was no significant evidence of publication bias. A subgroup analysis suggested more prominent effects of synbiotics among adults than infants and children for RTI prevention. The sensitivity analysis excluding trials with prebiotics or probiotics as controls was consistent with our primary analysis. This meta-analysis of clinical trials involving >10,000 individuals showed that synbiotic interventions could be an alternative nutrition strategy for conferring human health and preventing RTIs. Future investigations on the clinical efficacy and safety of synbiotic interventions are warranted with strain-specific and dose-specific approaches. *Adv Nutr* 2020;11:979–988.

Keywords: synbiotics, probiotics, prebiotics, respiratory tract infections, meta-analysis, RCT

Introduction

The human gastrointestinal tract harbors a complex network of commensal microbiota that constantly interact with the host immune system and influence the homeostasis of normal physiology and function. Growing evidence has shown that dysbiosis may confer susceptibility to gastrointestinal diseases, metabolic disorders, autism spectrum disorders, and cancers (1, 2). According to recent reports, the gut microbiota can be modified and manipulated by dietary components and antibiotics to achieve health benefits to hosts (2–4). Synbiotics, which are primarily composed of prebiotics and probiotics, are defined as a kind of dietary intervention approach to targeting gut microbiota, which is now gaining growing attention. Probiotics are live microorganisms that confer health benefits when administered in adequate amounts, with well-known examples of the genera *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* (5, 6). Prebiotics are compounds in foods providing nutrition for the growth of beneficial microorganisms, which include, but are not limited to, inulin, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) (7). Since prebiotics cannot be easily digested by human gut enzymes, they can move towards the human large intestine to produce SCFAs and regulate microbial fermentation, thereby modulating gut microbial homeostasis and the immune system (7). Synbiotics are a combination of pro- and prebiotics in an attempt to achieve either synergistic or complementary effects against multiple diseases, from gastrointestinal diseases such as antibiotic-associated diarrhea to noncommunicable diseases such as obesity and type 2 diabetes (7, 8).

Respiratory tract infections (RTIs) are a series of clinical syndromes covering the common cold, rhinitis, nasopharyngitis, bronchitis, epiglottitis, laryngitis, tracheitis, tracheobronchitis, pneumonia, and other upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs) (9). Most RTIs are of viral etiology but are often mistreated with antibiotics. Reports have suggested that only 25% of annual antibiotic prescriptions for the treatment of RTIs in the United States are appropriate (10), although >70% of viral RTIs in developing countries are treated with antibiotics (11). With the beneficial effects of probiotics and prebiotics on the human immune system, synbiotics can be a potential nutrition strategy to tackle the global issue of respiratory infections and misuse of antibiotics on RTIs. For instance, Wang et al. (12) reported that probiotics resulted in an 11% reduction in the number of children having RTIs. Additionally, a meta-analysis of 12 trials reported a 47% risk reduction of acute URTIs, shorter episode duration, and lower antibiotic prescription rate by probiotics (13). However, few meta-analyses have focused on the combined effect of prebiotics and probiotics on the prevention of RTIs.

To the best of our knowledge, this is the first systematic review and meta-analysis of clinical trials to examine the efficacy of synbiotic interventions for preventing RTIs.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A checklist pertaining to the items reported in this review is available in **Supplemental Table 1**.

Protocol and registration

The protocol of this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/, ID: CRD42018107637) on 5 September 2018.

Eligibility criteria

The meta-analysis included randomized controlled trials (RCTs) and placebo-controlled trials on synbiotics in the prevention of RTIs defined by the WHO *International Classification of Diseases, 11th revision* (9), among individuals of any age (including full-term infants) with no pretrial symptoms. Synbiotics were all administered through oral ingestion and composed of ≥1 probiotic bacterial strain plus ≥1 type of prebiotics in different forms, such as powdered milk, yogurt, or capsules. Studies were excluded if the participants had physician-diagnosed health conditions, were under immunocompromised status, or had taken any probiotics/prebiotics/synbiotics/antibiotics before the trial. In addition, studies were excluded if they did not use synbiotics (a combination of prebiotics and probiotics) in the intervention group or did not measure RTIs as primary or secondary outcomes. Moreover, conference abstracts, studies with the full text unavailable, studies not published in English, and unpublished studies were also not included.

Study identification and data extraction

Electronic searches were independently performed by 2 reviewers (CKYC and JT) from July 2018 to April 2019 on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://scholar.google.com). A detailed search strategy is available in **Supplemental Table 2**. Disagreements were resolved by discussion with a third reviewer (HP). Reference lists of eligible studies and reviews were manually screened to identify additional trials. Completed or ongoing trials were searched on ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp). Each identified article was initially screened by title and abstract, followed by an assessment of the full text for eligibility. Relevant information was extracted from the eligible studies and included the author, publication year, participants (age, sex, and inclusion and exclusion criteria), study design, interventions (types, doses of synbiotics, administration form, duration, and placebo), results (RTI case proportion or incidence), and funding sources. With regard to studies carried out in multiple phases, if the study recruited different participants in each phase, they were considered independent studies in our meta-analysis.

Risk-of-bias assessment for individual studies

The quality of the included studies was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1) (14). Published articles, supplementary materials, and protocols (where available) were assessed for 6 domains (random-sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and other sources of bias).

Statistical analysis

The proportion and incidence of RTI cases in the intervention and control arms were defined with the RTI cases and episodes by the intention-to-treat (ITT) approach (15). In other words, all participants were analyzed according to the assigned intervention and control arms, regardless of their completion or whether they dropped out of the study. The primary outcomes were defined as the number of participants who experienced ≥1 RTI episode or the total number of RTI episodes in both arms. The outcome measurements were the risk ratio or rate ratio of RTIs in the synbiotic-treated group compared with the placebo group. Other outcome measurements, such as disease severity, duration, or time to onset, were not considered in the quantitative analysis due to study heterogeneity. Counts of RTI events and patients extracted from publications were first converted into risks or rates according to chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions, version 5.2* (16). The risk ratio was calculated as the proportion of participants who experienced RTIs at least once in the synbiotic-treated group divided by the proportion of participants who experienced RTIs in the placebo group during the follow-up. The rate ratio was calculated as the incidence rate (number of RTI events per person per week) in the synbiotic-treated group
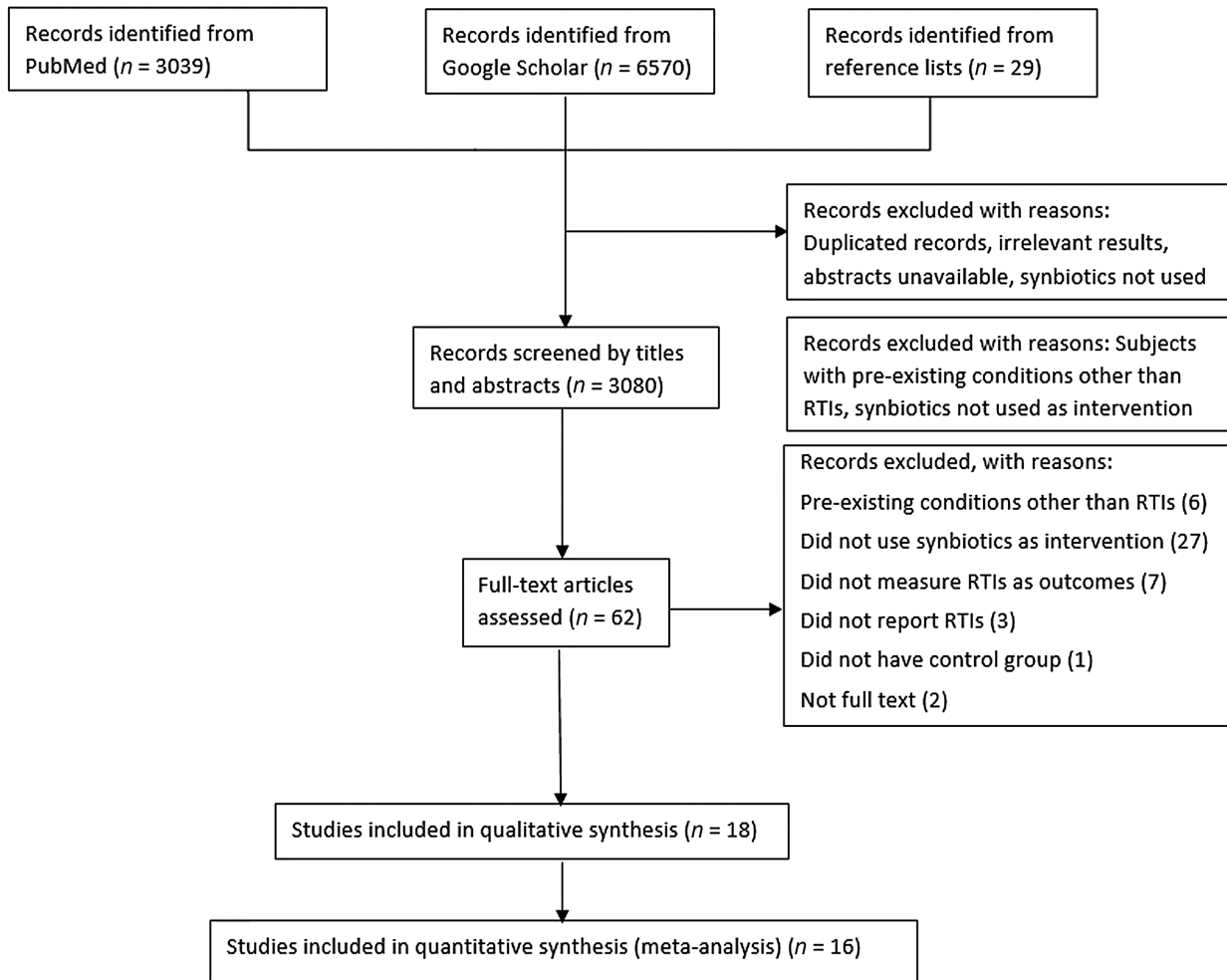
FIGURE 1 Flow diagram of the literature search. RTI, respiratory tract infection.

divided by the incidence rate in the placebo group during the follow-up period. The SE of the risk/rate ratio was calculated by $\sqrt{((1/Ee) + (1/Ec) - (1/Te) - (1/Tc))}$, where Ee and Ec referred to the number of RTI cases/episodes and Te and Tc referred to the total number of participants/episodes in the synbiotic and control groups, respectively. The estimates of risk ratio and rate ratio were summarized in a random-effects model using the inverse-variance weighting method for each study. The risk ratio and rate ratio of individual studies and their corresponding pooled estimates are presented in forest plots. Cochran's Q test (at a significance level of 0.05) was used to assess the heterogeneity among studies. Variation across studies was estimated by the I^2 statistic (the proportion of variability attributed to heterogeneity rather than chance). I^2 statistics <25%, 25–50%, and >50% were considered to represent low, moderate, and substantial levels of heterogeneity (17). Publication bias was detected by asymmetry in the funnel plot on visual inspection and by Egger's test (18). Subgroup analyses were carried out in the subgroup of infants (<12 mo of age), children (1–18 y old), and adults (>18 y old) to test the efficacy of the

synbiotic intervention in different age groups. Furthermore, the effect of intervention duration was investigated by random-effects meta-regression and presented in dotted-line plots with 95% CIs (19). A sensitivity analysis for trials using pure placebo as the control group was carried out. The leave-one-out sensitivity analysis was carried out to evaluate the impact of each study on the overall estimate (20). Data analysis and figure plotting were performed in R (version 3.5.1) and RevMan 5.0 software (Cochrane Collaboration).

Results

Study selection and characteristics
The study selection process is shown in **Figure 1**. The initial search from PubMed, Google Scholar, and the reference lists of published reviews yielded 9638 records, which were screened by titles and abstracts, where duplicate records and irrelevant results were removed. The remaining 3080 records were further screened by the eligibility criteria. After excluding 3018 studies with inconsistent objectives

and unavailable full text, 62 studies remained, which were primarily considered eligible and screened by the full text. Finally, 18 studies were included in the qualitative analysis, and 16 articles involving 10,443 individuals were included in the quantitative analysis. Multistage trials involving different participants at each stage were included as independent studies in our meta-analysis (21), whereas multistage trials involving the same population for consecutive periods were included only once in the meta-analysis (22). The characteristics of the individual studies included in the meta-analysis are shown in **Table 1**, where the location, participants, treatment and duration, outcomes, and results are summarized. A detailed version is available in **Supplemental Table 3**. The 18 studies included were published between 2007 and 2017, with 12 conducted in Europe, 3 in Asia, and 3 without reported locations. Two studies reported the effects of synbiotics in adults, 4 studies focused on children (from 1 to 18 y old), and the remaining included infants ≤12 mo of age. The duration of synbiotic supplementation in the included trials ranged from 2 wk to 1 y. The synbiotics mainly consisted of probiotics (e.g., *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, or a mixture strain) and prebiotics (e.g., FOS, GOS, inulin, or a mixture composition). The control group was offered capsules with sucrose, maltodextrin, microcrystalline cellulose, starch, standard formula or milk, and probiotics or prebiotics. The form of administration varied greatly and included capsules, tablets, infant formula, yogurt drinks, and powder dissolved in water, milk, or juice. The outcome included "common cold," "URTI," "LRTI," and "acute respiratory infection". One study measured acute otitis media (AOM; which is not classified as an RTI) as the primary endpoint and LRTIs as the secondary endpoint. Therefore, LRTI data from this study were included in the meta-analysis. Although the data extraction was performed using the ITT approach, it should be noted that the overall drop-out rate of eligible studies ranged from 1.25% (23) to 40.6% (22). In addition, 11 of the 16 studies were sponsored by or had authors employed by nutrition and food companies.

Synthesis of results
Nine studies ($n = 2845$) reported the number of participants who experienced ≥1 RTI episode in both arms according to the ITT approach. Compared with placebo, synbiotics reduced the rate of RTIs by 16% (rate ratio: 0.84; 95% CI: 0.73, 0.96; **Figure 2**). However, there was moderate heterogeneity among the studies ($Q = 17.08$, $P = 0.07$; $I^2 = 43.8\%$). Seven studies ($n = 7273$) reported the proportion of participants experiencing RTIs in both arms according to the ITT approach. Compared with placebo, synbiotics reduced the risk of developing an RTI by 16% (risk ratio: 0.84; 95% CI: 0.74, 0.95; **Figure 3**). Similarly, there was moderate heterogeneity among studies ($Q = 12.51$, $P = 0.05$; $I^2 = 47.7\%$).

Risk of bias within and across studies
The risks of bias of the individual studies were assessed and are presented in **Supplemental Figure 1**. Visual inspection of the funnel plot (**Supplemental Figure 2**) did not suggest publication bias. Egger's test for the asymmetry of the funnel plot did not suggest significant evidence of publication bias ($P = 0.20$ for the RTI rate ratio and $P = 0.55$ for the RTI risk ratio).

Additional analysis
Subgroup analyses on the RTI incidence in infants/children and adults were performed and are presented in **Figure 4**. The protective effects against RTI episodes were significant in adults (rate ratio: 0.68; 95% CI: 0.57, 0.81) but not in infants and children (rate ratio: 0.96; 95% CI: 0.85, 1.08).

The sensitivity analysis that excluded trials with prebiotics or probiotics as controls was consistent with our primary analysis (**Supplemental Figure 3**); the rate ratio (95% CI) with the synbiotic interventions was 0.73 (0.63, 0.84), and the risk ratio (95% CI) was 0.83 (0.73, 0.95). A leave-one-out sensitivity analysis was performed to examine individual study effects on the meta-analysis. For studies reporting the incidence of RTIs, the overall estimate of rate ratios (95% CIs) ranged from 0.81 (0.70, 0.93) to 0.88 (0.779, 0.997) in the leave-one-out sensitivity analysis (21, 32). Similarly, for studies reporting the RTI proportions, the overall estimate of risk ratios (95% CIs) ranged from 0.79 (0.70, 0.89) to 0.88 (0.79, 0.99) in the leave-one-out sensitivity analysis (15, 27). The results of the leave-one-out sensitivity analysis provided robust evidence for the preventive effects of synbiotic treatment against RTIs given that the overall estimates were significant after excluding any single study from the meta-analysis.

Discussion
This systematic review and meta-analysis revealed preventive effects of synbiotics against RTIs. Synbiotic intervention reduced the incidence of RTIs and the proportion of RTI cases by 16%. The potential preventive effects of synbiotics against RTIs might be attributed to their anti-inflammatory properties, which have already been discovered in gastrointestinal diseases but have not yet been widely reported in the respiratory system (36, 37). Subgroup analysis suggested significant protection in adults (rate ratio: 0.68; 95% CI: 0.57, 0.81). However, a similar subgroup analysis in children or infants (rate ratio: 0.96; 95% CI: 0.85, 1.08) did not yield significant findings. Overall, the study results showed moderate heterogeneity, and funnel plots did not suggest evidence of publication bias.

The overall results were in line with the positive findings on probiotics, but the magnitude and effects on subgroups differed. Hao et al. (13) reported a larger risk reduction in URTIs (47%), whereas the effect was only significant in children (OR: 0.43; 95% CI: 0.29, 0.63) but not in adults, and the episode rates of URTIs did not differ significantly between synbiotic and control groups. However, in our study, both the confidence intervals of rate ratios and risk ratios did not exceed 1. However, Hao et al. (13) included only 1 study with

TABLE 1 Characteristics of individual studies included in meta-analysis[1]

First author, year (ref)	Location	Participants	n	Outcome(s)	Treatment duration	Probiotic(s)	Prebiotics	Administration form	Results
Synbiotics vs. control									
Auinger, 2013 (24)	Germany	Adults	162	Common cold infections	16 wk	*Saccharomyces cerevisiae*	(1,3)-(1,6)-β-Glucan	Capsule	19% less RTI incidences, no significant improvement in severity
Cazzola, 2010 (25)	France	3- to 7-y-old children	135	Winter diseases	3 mo	*Lactobacillus helveticus, Bifidobacterium infantis, Bifidobacterium bifidum*	FOS	Dissolved powder	25% risk reduction in winter diseases
Cohen, 2013[2] (26)	France	7- to 13-mo-old infants	224	AOM, LRTIs, antibiotic treatment	12 mo	*Streptococcus thermophilus, Streptococcus salivarius, Lactobacillus rhamnosus*	Raftilose/raftiline	Infant formula	No significant effects
Gerasimov, 2016 (23)	Ukraine	3- to 12-y-old children	240	Acute RTIs	2 wk	*Lactobacillus acidophilus, Bifidobacterium lactis*	FOS	Dissolved powder	No significant effects on incidences, reduced severity scores, and time to resolution
Kukkonen, 2008 (15)	Finland	Newborns	1018	RTIs, antibiotic uses	6 mo	*Lactobacillus rhamnosus, Bifidobacterium breve, Propionibacterium freudenreichii*	GOS	Capsule	Reduced RTIs (OR: 0.49) after, but not during, intervention
Panigrahi, 2017[2] (27)	India	Newborns	4556	LRTIs, sepsis, meningitis	7 d	*Lactobacillus plantarum*	FOS	Capsule	40% reduced risk of sepsis and death; 34% risk reduction in LRTI
Pregliasco, 2008a (21)	NR	Adults	237	RTIs	90 d	*Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis*	FOS	Dissolved powder	Reduced duration of RTIs by 0.97 d, reduced episodes and severity
Pregliasco, 2008b (21)	NR	Adults	234	RTIs	90 d	*Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis*	FOS	Dissolved powder	Reduced duration of RTIs by 0.97 d, reduced episodes and severity
Pregliasco, 2008c (21)	NR	Adults	250	RTIs	90 d	*Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis*	FOS and GOS	Dissolved powder	Reduced duration of RTIs by 0.97 d, reduced episodes and severity
Sazawal, 2010 (28)	India	1- to 3-y-old children	624	Pneumonia, common childhood diseases	1 y	*Bifidobacterium lactis*	Oligosaccharides	Infant formula	24% reduction in pneumonia, 35% reduction in severe acute LRTIs
Picaud, 2010[3] (29)	France	Infants	771	RTIs, infections, antibiotic uses	3 mo	*Bifidobacterium longum, Streptococcus thermophilus*	FOS	Infant formula	No significant effects on RTIs, reduced GI and overall infections
Puccio, 2007 (30)	Italy	Healthy infants	138	Weight gain, GI tolerability, RTIs	112 d	*Bifidobacterium longum*	FOS and GOS	Infant formula	A nonsignificant trend of LRTI incidences (28% vs. 43%) by synbiotics compared with control
Xuan, 2013[2] (31)	Vietnam	18- to 36-mo-old children	368	URTIs, LRTIs	5 mo	*Lactobacillus paracasei, Bifidobacterium longum*	Inulin + FOS	Follow-on formula	No significant effects
Synbiotic vs. probiotic									
Bocquet, 2013[2] (32)	France	Newborns	528	RTIs, infections, antibiotic uses	11 mo	*Bifidobacterium animalis* subsp. *lactis*	GOS + FOS	Milk formula	No significant effects
Synbiotic vs. prebiotic									
Gil-Campos, 2012 (33)	Spain	1-mo-old infants	137	RTIs, antibiotic uses	6 mo	*Lactobacillus fermentum*	GOS	Infant formula	No significant effects
Maldonado, 2010 (34)	Spain	6-mo-old infants	188	RTIs, other infections	6 mo	*Lactobacillus fermentum*	GOS	Follow-on formula	Reduced rates of RTIs, URTIs; no significant effects on LRTIs or otitis
Szajewska, 2017[2] (35)	Poland	Infants	182	RTIs	5 mo	*Lactobacillus* F19	FOS + GOS	Infant formula	66% risk reduction in LRTIs
Vlieger, 2009 (22)	Netherlands	Newborns	126	URTIs, antibiotic uses	3 mo	*Bifidobacterium* BB-12, *Lactobacillus paracasei*	GOS	Infant formula	No significant effects

[1] AOM, acute otitis media; FOS, fructo-oligosaccharides; GI, gastrointestinal; GOS, galacto-oligosaccharides; LRTI, lower respiratory tract infection; NR, not reported; Ref, reference; RTI, respiratory tract infection; URTI, upper respiratory tract infection.
[2] Multicenter study.
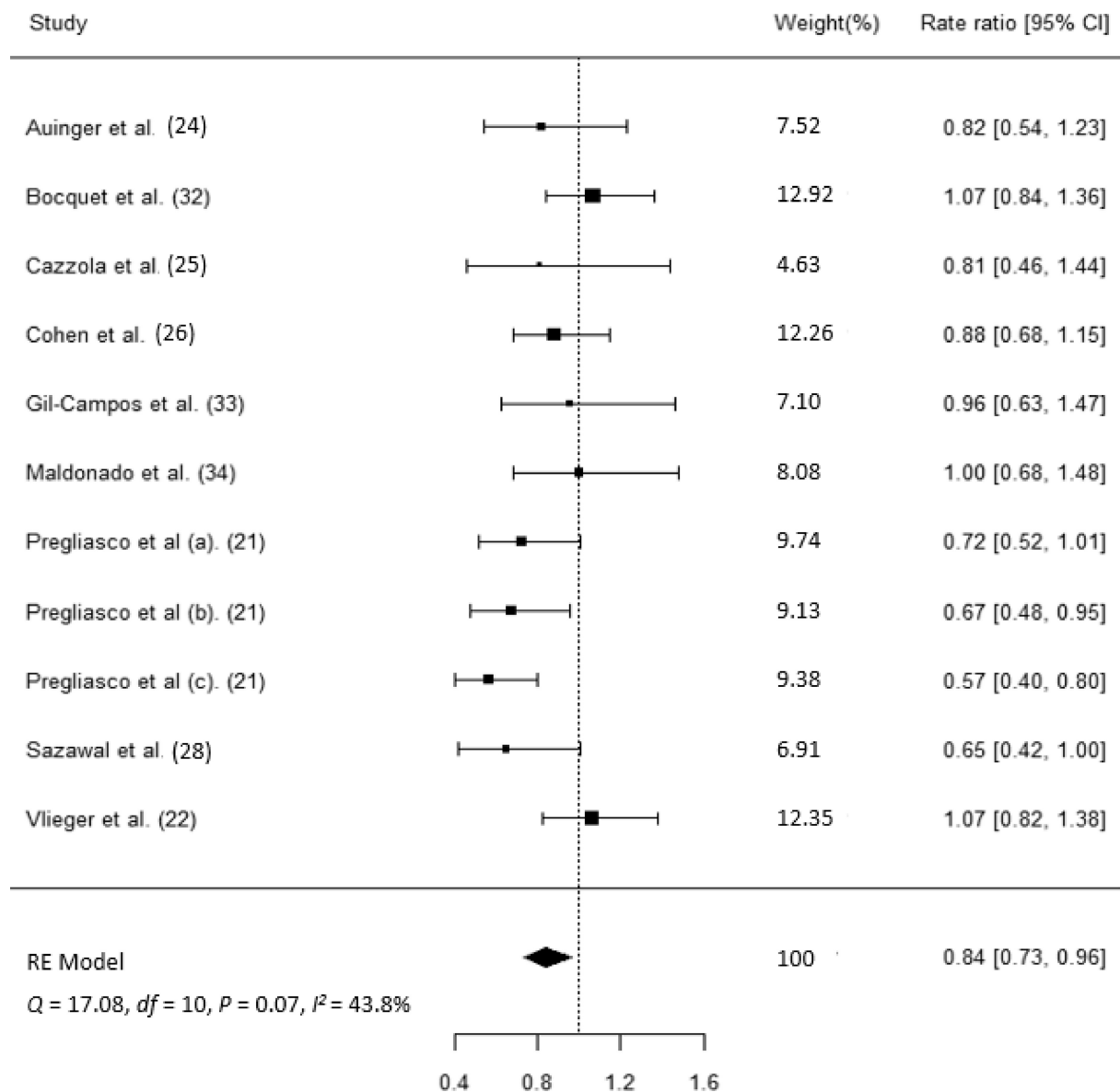[3] Open-label study.

FIGURE 2 Forest plot for the effects of synbiotic supplements on RTI incidence. RE, random effect; RTI, respiratory tract infection.

adults and did not further separate infants from children as in our review. The increased sample sizes of adult participants in our study could indicate increased power and showed protection for adults. In contrast, our review did not identify trials in the elderly population; thus, examining the effects of synbiotics compared with probiotics based on previous reviews was not feasible. We reported an RTI risk reduction similar to a study in children aged 0–18 y who received 10^8– 10^{11} CFU probiotics/d (12), although the authors included nasal spray as an additional administration route, which was not included in our study.

The duration of synbiotic supplementation can also influence the efficacy of this nutrition strategy. For instance, Panigrahi et al. (27) reported a one-third risk reduction in LRTIs among newborns taking *Lactobacillus plantarum* plus

FOS capsules for as few as 7 d, whereas consuming synbiotic-enriched infant formula (*Streptococcus thermophilus*, *Streptococcus salivarius*, *Lactobacillus rhamnosus* plus raftilose) for 1 y did not make a difference among infants at 7–13 mo of age (26). This phenomenon might be attributed to the fact that compositions of gut microbiota in infants are less stable and mature than those in older children/adults, thereby affecting the levels of susceptibility to microbiota modification (38).

The sensitivity analysis showed that the synbiotic intervention resulted in better preventive effects when compared with a placebo group than with prebiotic or probiotic groups. This was consistent with previous reports that prebiotics and probiotics might independently exert beneficial effects and exhibit a synergistic effect when administered
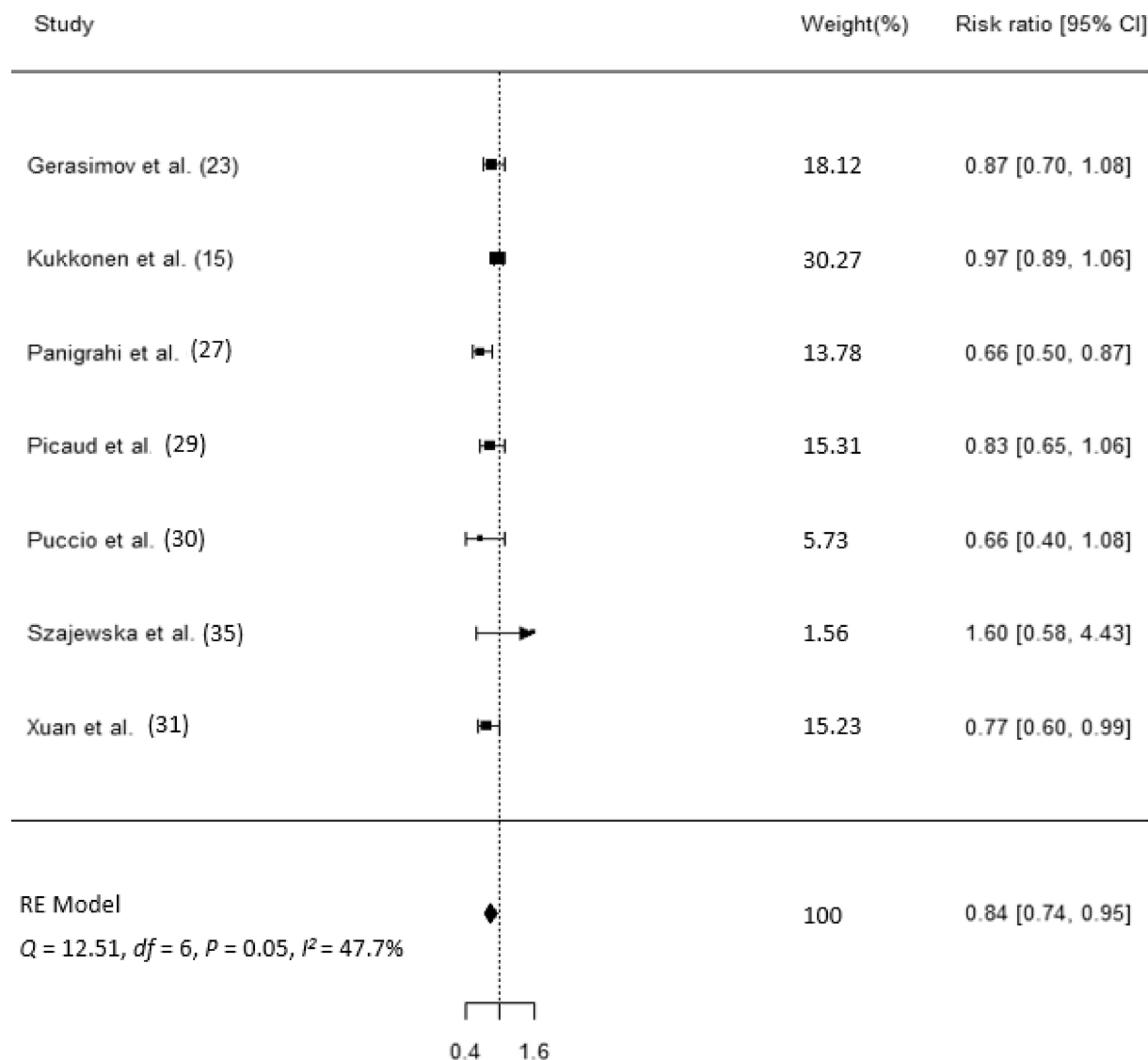
FIGURE 3 Forest plot for the effects of synbiotic supplements on the proportion of subjects with RTIs. RE, random effect; RTI, respiratory tract infection.

in combination (39). Our included studies contained a broad range of prebiotics, and the effectiveness of various types of prebiotics can be a potential area for future research (7).

The immunization history of participants would also affect the risk of contracting RTIs. Most included studies were in pediatric participants at ages eligible for immunization programs based on the country. Only 2 studies explicitly excluded participants vaccinated against influenza (23, 24), and 4 others reported a partial vaccination history of the participants (29, 32–34). In Cohen et al. (26), participants were vaccinated with 7-valent pneumococcal conjugate vaccines against *Streptococcus pneumoniae*, which caused AOM, pneumonia, and other RTIs. Nonetheless, the preventive effects of synbiotics against RTIs were still clearly observed, possibly because the clinical trials were mostly randomized,

and the immunization history should be balanced between the intervention and control arms.

Variations in the indigenous microbiota of participants also accounted for variations in the results. Previous studies have suggested host-specific responses to probiotics (40). Resistance to probiotic interventions was observed in colonized but not germ-free mice (40, 41), which suggested that the indigenous microbiota might mediate murine resistance to probiotics. Similarly, human participants also demonstrated "permissive" and "resistant" phenotypes to multistrain probiotics, which could be predicted by host microbiome features or prior exposure to antibiotics or pathogens (42). Host responses could also be individualized by gastrointestinal metabolism and immune reactions (40). Given that synbiotics contain probiotics, it is probable that the baseline microbiota
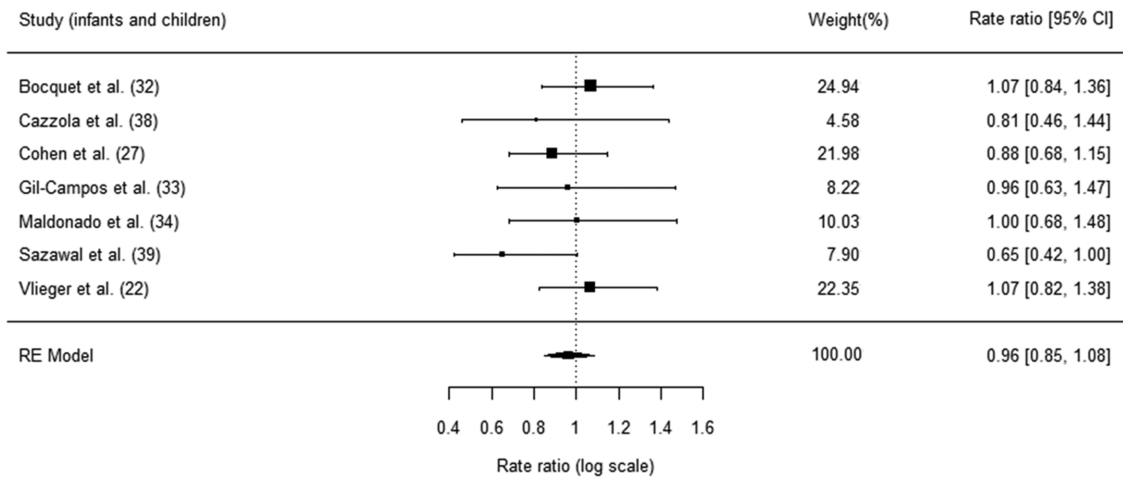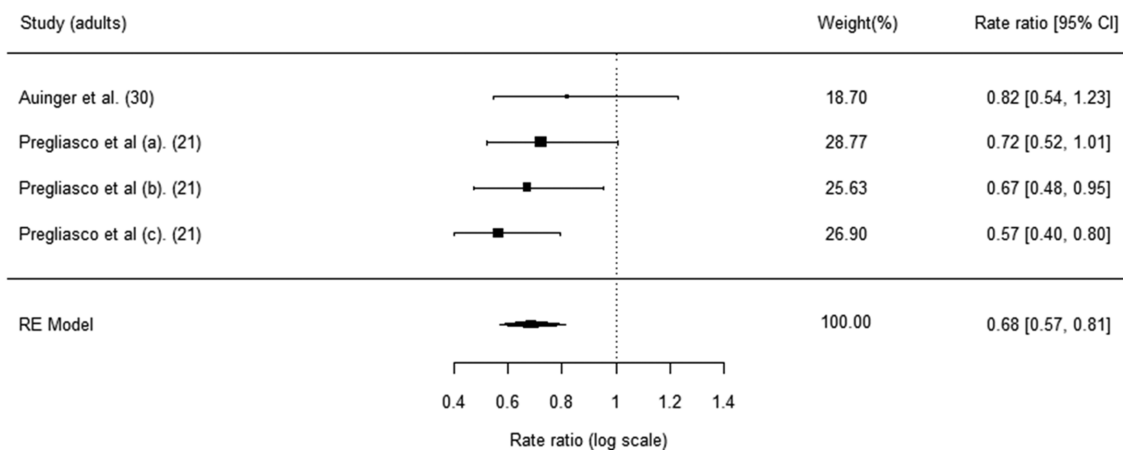
A

B

FIGURE 4 (A, B) Subgroup analysis for RTI incidence among the different age groups. RE, random effect; RTI, respiratory tract infection.

also modulates responses to synbiotic supplements in this meta-analysis.

In our review, the side effects of synbiotic intervention were mild gastrointestinal conditions, such as loose stools and abdominal discomfort (26, 27). For instance, a greater predisposition to liquid stools in infants receiving synbiotics might be attributable to the prebiotic components, which have effects that are similar to those of dietary fibers, such as increasing fecal bulk and frequency and alleviating constipation (43, 44). Moreover, prebiotics at a higher dose (>15 g oligosaccharides or 31–41 g oligofructose/d) were also reported to induce flatulence, abdominal pain, bowel contraction, liquid stools, and bloating in adults (45). The prebiotic doses used here were much lower (≤1 g/d), but the upper limit of tolerable doses in children is still unclear. Additionally, some studies did not define or report any adverse effects (AEs), which called attention to the need for more transparent and consistent AE assessments in clinical trials of synbiotics.

To our knowledge, our study is the first systematic review and meta-analysis of RCTs on synbiotic interventions to prevent RTIs. Nevertheless, our study has several limitations. First, the generalizability to healthy elderly individuals might not be appropriate given the limited number of studies examining the elderly population. In addition, it was difficult to compare the specific type and dose of synbiotics, as most included trials did not provide head-to-head comparisons. Moreover, the observed beneficial effects cannot be differentiated from synergistic or complementary synbiotic mechanisms due to the variance in control groups ranging from placebo to prebiotics/probiotics. Last, most included trials were conducted in individuals with European ancestry.

To conclude, this systematic review and meta-analysis suggests benefits of synbiotics in preventing RTIs without previously diagnosed symptoms. This potential application could indirectly reduce antibiotic misuse in treating RTIs and alleviate the global burden of antimicrobial resistance. Future investigations on the clinical efficacy and safety of synbiotic

interventions are warranted with strain-specific approaches and consistent methodology.

Acknowledgments

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