

Role of *Lactocaseibacillus rhamnosus* GG in the Management of Respiratory Diseases: A Systematic Review and Meta-Analysis

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ABSTRACT: Respiratory diseases represent a significant global health issue. Currently, there is growing interest in using probiotics [e.g., *Lactocaseibacillus rhamnosus* GG (LGG)] as adjunctive therapies for the management of respiratory diseases. However, the efficacy of LGG in respiratory diseases remains unknown. Therefore, this study aimed to evaluate the effectiveness of LGG in preventing and treating respiratory diseases. A comprehensive literature search was performed using the PubMed, Embase, Cochrane Library, and Scopus databases using keywords related to LGG and respiratory diseases. Studies were selected on the basis of predefined inclusion and exclusion criteria, and data were extracted for qualitative and quantitative analyses. The Cochrane Risk of Bias tool was used to assess the methodological quality of the included studies, and RevMan 5.4 was used to perform the meta-analysis. Out of 155 studies that were initially identified, 13 randomized controlled trials met the inclusion criteria. The meta-analysis showed that LGG intervention, both as a preventive and therapeutic strategy, significantly reduced the incidence of respiratory disease episodes (mean difference: -0.14 , 95% confidence interval: -0.27 to -0.01 , $P=0.03$) and mitigated associated symptoms compared with placebo or no intervention. The results of subgroup analyses indicated that LGG was particularly effective in reducing the duration and severity of respiratory infections in children and high-risk populations. However, heterogeneity ($I^2=62\%$) was observed, which was likely because of variations in the study design, dosage, and patient populations. These findings suggest that LGG may be a promising adjunctive therapy for respiratory diseases, particularly in preventive settings.

Keywords: diet therapy, *Lactocaseibacillus rhamnosus*, preventive therapy, probiotics, respiratory tract diseases

INTRODUCTION

Respiratory diseases represent a substantial global health burden. They encompass conditions ranging from the common cold to more severe respiratory infections, chronic obstructive pulmonary disease, and asthma. These diseases are typically managed using medications, lifestyle modifications, and at times supportive therapies. Recently, probiotics have gained attention as a potential adjunctive therapy for respiratory diseases because of their ability to modulate the gut microbiota and influence the immune system (Balta et al., 2021; Du et al., 2022; Mathipa-Mdakane and Thantsha, 2022).

Probiotics are microorganisms that have positive effects on the host. They have been extensively studied for their role in modulating the immune system and providing var-

ious health benefits, especially in the management of respiratory diseases (Mathipa-Mdakane and Thantsha, 2022). To confer health benefits, probiotics should be non-pathogenic to the host, protect against pathogenic microorganisms, and prevent antibiotic resistance (Ouweland et al., 2016). As one of several probiotic microorganisms that have been well documented for their ability to inhibit the adherence and growth of several pathogens, *Lactocaseibacillus rhamnosus* strain GG (LGG) was isolated from healthy human feces by Gorbach and Goldin (Du et al., 2022). LGG has been shown to reduce many proinflammatory cytokines [e.g., tumor necrosis factor alpha, interleukin (IL)-1 β , IL-6, and interferon gamma] and various chemokines (e.g., CCL2, CCL3, CCL5, CCL7, CCL20, and CXCL8) (Han et al., 2021). Moreover, LGG has been hypothesized to reduce the severity and duration of respi-

Received 10 December 2024; Revised 7 April 2025; Accepted 11 April 2025; Published online 30 June 2025

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ratory infections, enhance the immune response, and mitigate inflammation in the respiratory tract (Lehtoranta, 2012; Ouwehand et al., 2016; Han et al., 2021). Several clinical studies have investigated the efficacy of LGG in individuals with respiratory diseases, but the results have been mixed (Hojsak et al., 2010a, 2010b; Kumpu et al., 2012, 2013; Tapiovaara et al., 2016; Bruzzese et al., 2018; Hojsak, 2018; Kara et al., 2019; Damholt et al., 2022; Wischmeyer et al., 2024).

In addition, the gut-lung axis plays a crucial role in respiratory health. The composition of the gut microbiota influences immune function, and dysbiosis has been linked to respiratory conditions. Supplementation with probiotics, including *Bifidobacterium breve*, *Lactobacillus reuteri*, and *Lactobacillus casei* strains, has been investigated for its potential effects on respiratory health. Compared with other probiotic strains, LGG has unique properties, including its ability to survive the stomach's acidic environment and adhere to intestinal epithelial cells, which may enhance its immunomodulatory effects (Chunxi et al., 2020). However, there are limited studies that specifically evaluated the effectiveness of LGG in respiratory disease management.

Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy of LGG in the prevention and treatment of respiratory diseases, synthesizing evidence from clinical trials to provide a comprehensive understanding of its role in respiratory health.

MATERIALS AND METHODS

Literature search

This study conducted a systematic and comprehensive literature search in the PubMed, Embase, Cochrane Library, and Scopus databases. The literature search was

performed from January 2000 to December 2023 to ensure that recent and relevant studies were included. The search strategy included a combination of keywords and controlled vocabulary related to LGG, respiratory diseases, and clinical studies. The search was limited to human studies and had no restrictions for language: Lactocaseibacillus rhamnosus GG AND (treatment OR therapy OR management) AND (respiratory OR pulmonary).

Study criteria

Articles were selected on the basis of predefined inclusion and exclusion criteria. The inclusion criteria encompassed clinical studies investigating the use of LGG in individuals diagnosed with respiratory diseases. We considered randomized controlled trial (RCT) studies. Meanwhile, animal studies, studies not providing primary data (e.g., reviews and editorials), and studies using other probiotic strains or combination therapies were excluded.

Study selection

A total of 155 studies were initially identified. After removing 17 duplicates, the titles and abstracts of 138 studies were screened. Fifty articles were deemed eligible for full-text review, of which 37 did not meet the inclusion criteria. Ultimately, 13 studies were included in the qualitative and quantitative analysis. A PRISMA flowchart illustrating the study selection process is shown in Fig. 1.

Data extraction

This study extracted relevant data from the selected articles. This included information on the study design, sample size, patient characteristics, intervention details (e.g., dose, duration, and formulation of LGG), control groups, and outcomes.

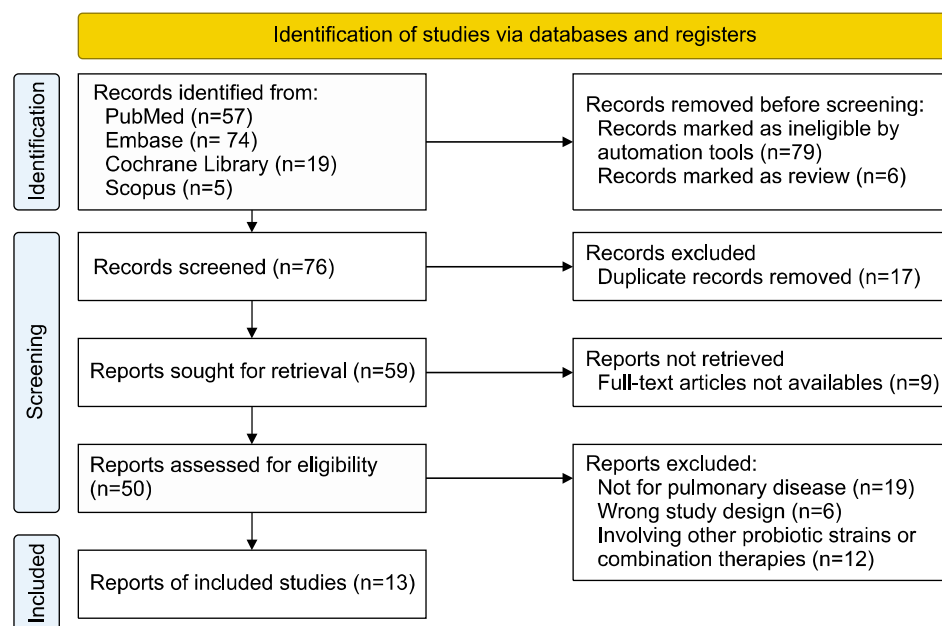


Fig. 1. Study selection using PRISMA.

Quality assessment

This systematic review and meta-analysis independently evaluated the risk of bias in the eligible studies using the Cochrane Risk of Bias tool for randomized trials (RoB 2), and the results were cross-validated. The risk of bias assessment involved the following domains: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of participants and operators (performance bias), blinding of outcomes assessment (detection bias), integrity of outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias (other bias).

Statistical analysis

The data obtained were processed using RevMan 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We performed meta-analyses to assess the respiratory disease events of LGG versus placebo by entering the mean \pm standard deviation to measure the mean difference [MD; 95% confidence interval (CI)]. The I^2 statistic was used to assess heterogeneity among studies. The fixed effects model was used if $I^2 < 50\%$, whereas the random effects model was used if $I^2 \geq 50\%$. The results were presented in a forest plot, and the overall effect was considered significant if $P < 0.05$.

RESULTS

Characteristics of the included studies

Thirteen studies examined the effectiveness of LGG interventions compared with placebo controls in populations with diverse health conditions. The studies used a RCT design with the double-blind method, with sample sizes varying from 59 to 742 participants and age ranges from infants to adults. The study objectives included preventing and treating various conditions, including upper respiratory tract infections, cystic fibrosis, asthma, respiratory tract infections, common colds, and coronavirus disease 2019 (COVID-19). The intervention duration varied from 72 h to 12 months, with LGG doses ranging from 1×10^8 colony-forming units (CFU)/mL to 2×10^{10} CFU/mL. The placebo controls used in the studies included maltodextrin, gelatin capsules, certain foods, milk-based beverages, oral juices, and sterile water. The results from the studies suggest that LGG can reduce the incidence of respiratory tract infections and other health conditions tested. The characteristics of the included studies are outlined in Table 1 (Kekkonen et al., 2007; Moreira et al., 2007; Hojsak et al., 2010a, 2010b; Morrow et al., 2010; Kumpu et al., 2012, 2013, 2015; Tapiovaara et al., 2016; Bruzzese et al., 2018; Kara et al., 2019; Damholt et al., 2022; Wischmeyer et al., 2024).

Quality assessment

The risk of bias assessment using RevMan 5.4 indicated that, overall, all studies had a low risk of bias, as depicted in Fig. 2. However, in terms of outcome assessment blinding, most studies showed a higher risk because some studies did not use a triple-blind methodology (Fig. 2).

Meta-analysis results

Effects of LGG in the management of respiratory diseases: The meta-analysis results derived from 13 RCTs found that patients receiving LGG intervention, both preventively and therapeutically, showed reduced exacerbations and incidence of lung disease episodes compared with the control group (MD: -0.14 , 95% CI: -0.27 to -0.01 , $P=0.03$). In addition, the forest plot results showed heterogeneity above 50% among the included studies ($P=0.002$, $I^2=62\%$). Hence, a random effects model was chosen for our analysis (Fig. 3).

Publication bias: Because of the high heterogeneity in our forest plot, we created a funnel plot (Fig. 4), demonstrating a symmetric distribution of studies. Therefore, this meta-analysis can be interpreted as having a low risk of publication bias based on the included studies.

DISCUSSION

This systematic review and meta-analysis evaluated the efficacy of LGG in the management of respiratory diseases, synthesizing evidence from 13 RCTs. The findings demonstrate that LGG, both as a preventive and therapeutic intervention, significantly reduces the incidence of respiratory disease episodes and mitigates associated symptoms compared with placebo or no intervention. The observed MD (-0.14 , 95% CI: -0.27 to -0.01 , $P=0.03$) suggests a modest but clinically meaningful benefit, particularly in reducing the frequency of respiratory exacerbations and improving patient outcomes. These results align with the growing body of evidence supporting the role of probiotics in modulating immune responses and enhancing respiratory health through the gut-lung axis (Du et al., 2022; Mathipa-Mdakane and Thantsha, 2022).

The reduction in respiratory disease episodes and symptoms observed in this meta-analysis has important clinical implications. LGG supplementation could translate to fewer sick days, reduced healthcare visits, and improved quality of life for patients, particularly those at high risk of respiratory infections (e.g., children, the elderly, and individuals with chronic respiratory conditions). For example, Hojsak et al. (2010b) demonstrated that children receiving LGG had a significantly lower risk of respiratory tract infections lasting more than 3 days compared with the placebo group (odds ratio: 0.57,

Table 1. Characteristics of the included studies (n=13)

Study	Study design	Number of participant	Age (years)	Purpose of intervention	Duration of intervention	Intervention (LGG)	Control (placebo)	Medical condition	Outcome
Bruzzese et al. (2018)	RCT, DB	95	2–16	Treatment	12 months	6×10 ⁹ CFU/mL	163 mg maltodextrin + 75 mg gelatin capsule + 2 mg magnesium stearate	Cystic fibrosis	The mean number of pulmonary exacerbations was 2.3±2.1 in the LGG group and 2.2±1.7 in the placebo group (OR: 1.21, 95% CI: 0.58-2.52; <i>P</i> =0.616).
Damholt et al. (2022)	RCT, DB	619	2–6	Treatment	16 weeks	1×10 ⁹ CFU/mL+ predefined food	Predefined food (fruit compote/ cereal+milk/ chocolate milk/ milk/water)	Upper respiratory tract infection	A statistically significant difference was found between cluster 1 and cluster 2 in terms of treatment (<i>P</i> =0.0327) with a higher percentage of children receiving LGG DSM 33156 in cluster 2 (178 of 309, 57.6%) than in cluster 1 (131 of 309, 42.4%). Cluster 1 was characterized by a high number of days with URTI episodes, whereas cluster 2 showed mild URTI symptoms.
Hojasak et al. (2010a)	RCT, DB	281	1–7	Preventive	3 months	1×10 ⁹ CFU/mL+ 100 mL fermented milk	100 mL fermented milk	Respiratory tract infection	The number of respiratory infections lasting longer than 3 days was 39 (28.1%) in the LGG group and 70 (49.3%) in the placebo group (OR: 0.57, 95% CI: 0.41–0.78; <i>P</i> <0.001).
Hojasak et al. (2010b)	RCT, DB	742	>1	Preventive	7 months	1×10 ⁹ CFU/mL+ 100 mL fermented milk	100 mL fermented milk	Respiratory tract infection	Patients in the LGG group had a lower risk for episodes of respiratory tract infections that lasted 3 days (2.1%) than those in the placebo group (5.2%) [relative risk: 0.4 (95% CI: 0.2–0.9); number needed to treat: 33 (95% CI: 17–257)].
Kara et al. (2019)	RCT, DB	100	0.5–5	Preventive	3 months	1×10 ⁹ CFU/mL+ diet + breast milk <2 years	Diet+breast milk <2 years	Respiratory tract infection	After 3 months of control, the number of upper respiratory infections at the 3rd month was 0.73±0.49 in the LGG group and 0.27±0.51 in the placebo group (<i>P</i> <0.034).
Kekkonen et al. (2007)	RCT, DB	141	22–69	Preventive	3 months	2×10 ¹⁰ CFU/mL	2×65 mL milk-based fruit drink	Upper respiratory tract infection	Patients in the LGG group had fewer episodes of upper respiratory tract infections (0.24) than those in the placebo group (0.73) (<i>P</i> <0.001).
Kumpu et al. (2012)	RCT, DB	501	2–6	Preventive	28 weeks	1×10 ⁸ CFU/mL+ Fresh milk 100 mL	Fresh milk 100 mL	Respiratory tract infection	The mean number of respiratory tract infections was 0.7 in the LGG group and 0.5 in the placebo group (<i>P</i> =0.32). The number of days with at least one respiratory symptom was 5.03/month (95% CI: 4.92–5.15) in the GG group and 5.17/month (95% CI: 5.05–5.29) in the placebo group (incidence rate ratio: 0.97, 95% CI: 0.94–1.00; <i>P</i> =0.098).

Table 1. Continued

Study	Study design	Number of participant	Age (years)	Purpose of intervention	Duration of intervention	Intervention (LGG)	Control (placebo)	Medical condition	Outcome
Kumpu et al. (2013)	RCT, DB	523	2–6	Treatment	28 weeks	1×10 ⁸ CFU/mL+ Fresh milk	Fresh milk 400 mL	Respiratory tract infection	The number of days per month (incidence rate) with at least one respiratory symptom was significantly lower in the LGG group than in the control group during the intervention period [6.48 (95% CI: 6.28–6.68) vs. 7.19 (95% CI: 6.98–7.41); <i>P</i> <0.0001]. The mean duration of respiratory symptom episodes related to a study physician visit was 16 days (95% CI: 13–19) in the LGG group and 18 days (95% CI: 14–23) in the control group (<i>P</i> =0.42).
Kumpu et al. (2015)	RCT, DB	60	18–65	Preventive	3 weeks	1×10 ⁹ CFU/mL+ 100 mL oral juice	1×100 mL oral juice	Common cold	Daily symptom scores on 5 days following inoculation were lowest in the live LGG group (mean area under the curve 2.88, 95% CI: 1.51–4.25), but with no statistical difference compared with the control group (4.11, 95% CI: 2.77–5.44) (<i>P</i> =0.45).
Moreira et al. (2007)	RCT, DB	141	N/A	Treatment	3 months	3.0×10 ⁸ CFU/mL	2×65 mL milk-based fruit drink	Asthma	No differences in changes of blood eosinophil numbers, serum eosinophil cationic protein, total IgE, and Phadiatop were observed between the LGG and placebo groups.
Morrow et al. (2010)	RCT, DB	146	≥19	Preventive	72 hours	2×10 ⁹ CFU/mL	Sterile water	VAP	Among the 138 patients in the modified intention-to-treat analysis, 50 were diagnosed with VAP using the clinical criteria and underwent nonbronchoscopic bronchoalveolar lavage [33/70 placebo patients (47.1% incidence; 95% CI, 35.1–59.1) vs. 17/68 patients treated with <i>Lactobacillus</i> (25.0% incidence; 95% CI, 14.4–35.6); <i>P</i> <0.0001].
Tapiovaara et al. (2016)	RCT, DB	59	18–65	Preventive + Treatment	3 weeks (preventive)+ 3 weeks (treatment)	1×10 ⁹ CFU/mL+ 100 mL oral juice	1×100 mL oral juice	Common cold	The LGG groups had the lowest HRV loads, whereas the placebo group had the highest HRV loads [log ₁₀ copies/mL, 95% CI, 6.20 (5.18–7.40) in live, 6.30 (4.91–7.08) in inactivated LGG, and 7.25 (5.81–7.52) in placebo, <i>P</i> =0.57 in day 2]. Participants receiving LGG were significantly less likely to report any symptoms by day 28 (26.4% vs. 42.9%, <i>P</i> =0.02). No participants reported new symptoms after day 28. Participants receiving LGG had a significantly prolonged time to onset of symptoms (log rank <i>P</i> =0.006). Decreased COVID-19 incidence was observed in participants randomized to LGG; this difference was not statistically significant (8.8% vs. 15.4%, <i>P</i> =0.17).
Wischmeyer et al. (2024)	RCT, DB	182	>1	Preventive	28 days	<5 years: 1×10 ¹⁰ 5 years: 2×10 ¹⁰	DSM capsules (1×325 mg microcrystalline cellulose)	COVID-19	

LGG, *Lactocaseibacillus rhamnosus* GG; RCT, randomized controlled trial; DB, double-blind; CFU, colony-forming units; URTI, upper respiratory tract infection; CI, confidence interval; OR, odds ratio; IgE, immunoglobulin E; VAP, ventilator-associated pneumonia; COVID-19, Coronavirus Disease 2019; HRV, human rotavirus.

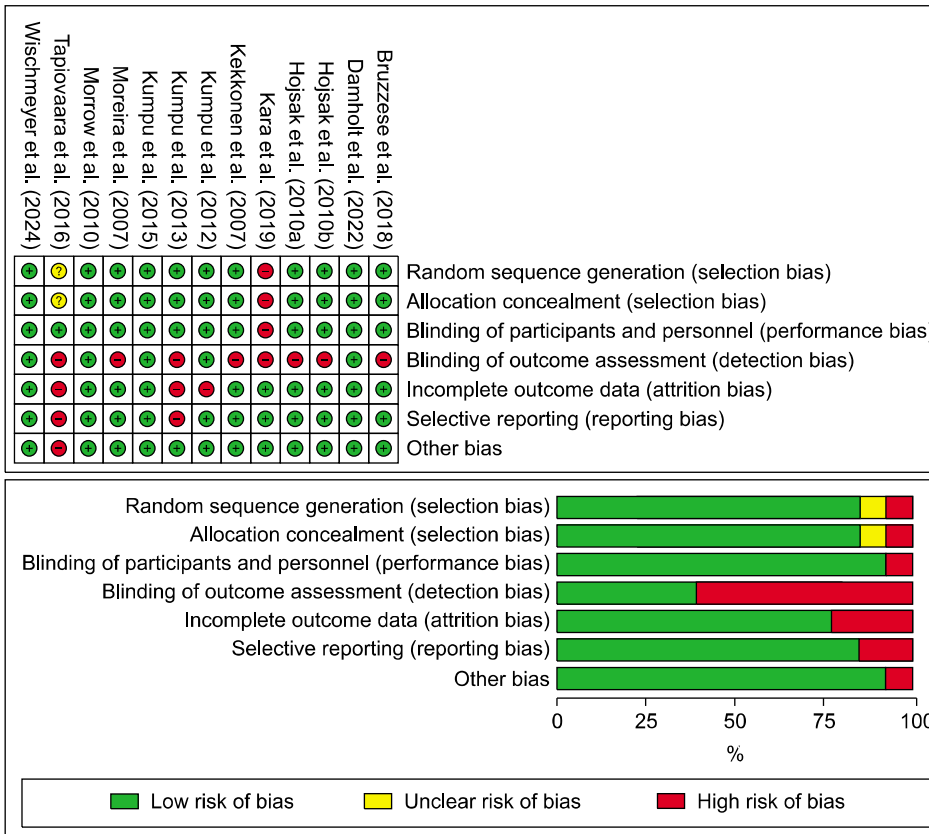


Fig. 2. Risk of bias assessment using the Cochrane Risk of Bias tool for randomized trials.

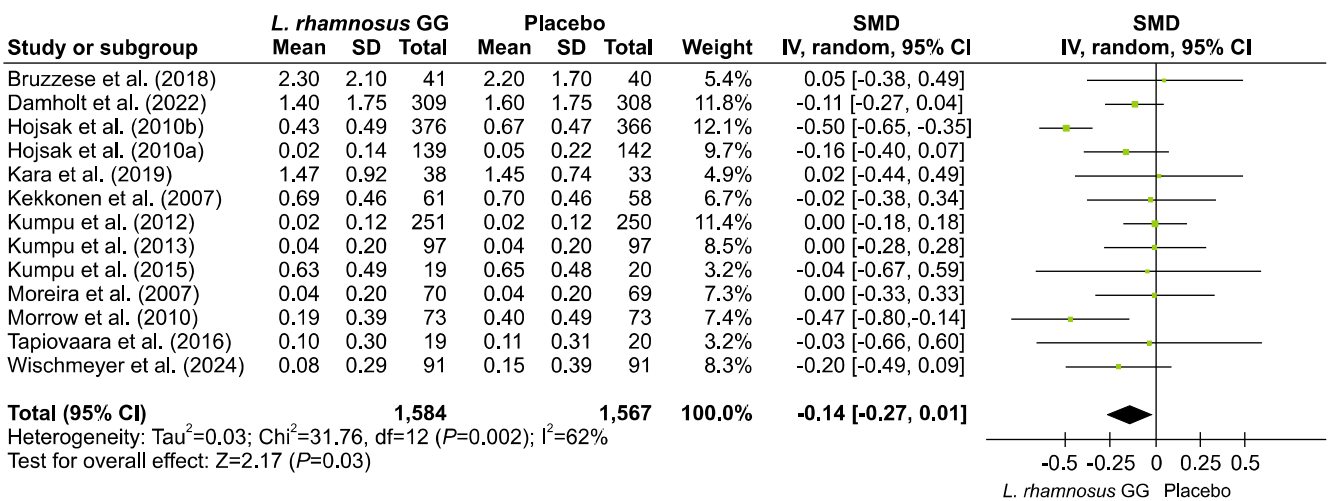


Fig. 3. Forest plot analysis of the effects of *Lactocaseibacillus rhamnosus* GG in the management of respiratory diseases. SD, standard deviation; CI, confidence interval; SMD, standard mean difference.

95% CI: 0.41 – 0.78, $P < 0.001$). Similarly, Wischemeyer et al. (2024) found that LGG significantly reduced the likelihood of COVID-19 symptoms when used as post-exposure prophylaxis, highlighting its potential as a preventive strategy in high-risk populations.

Although statistically significant, the modest MD (–0.14) observed in this meta-analysis underscores the need for careful consideration of the role of LGG in clinical practice. Although the effect size is small, it may still be meaningful in populations with a high burden of respiratory diseases, where even a slight reduction in

disease incidence or severity could lead to substantial public health benefits. However, further studies are needed to determine the optimal dosage, duration, and patient populations for LGG intervention (Balta et al., 2021; Mazziotta et al., 2023).

The meta-analysis revealed considerable heterogeneity among the included studies ($I^2 = 62\%$, $P = 0.002$), which may limit the findings’ generalizability. This heterogeneity can be attributed to several factors, including variations in the study design, patient populations, LGG dosage, and intervention duration. For example, the dosage

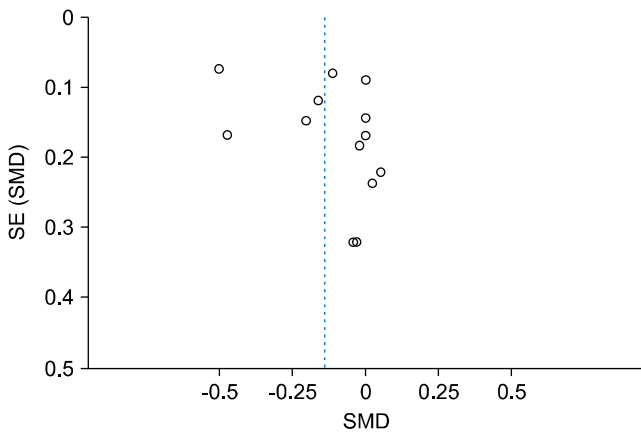


Fig. 4. Funnel plot analysis. SE, standard error; SMD, standard mean difference.

of LGG ranged from 1×10^8 CFU per day to 2×10^{10} CFU per day across studies, and the intervention duration varied from 72 h to 12 months. In addition, differences in the definition of respiratory disease outcomes and the use of diverse placebo controls (e.g., maltodextrin, milk-based beverages, or sterile water) may have contributed to the variability in the results (Kumpu et al., 2012, 2013).

To address these issues, future studies should aim to standardize key variables, including the LGG dosage, intervention duration, and outcome measures. Furthermore, subgroup analyses based on patient age, underlying health conditions, and disease severity could help identify the populations that may benefit most from LGG intervention. For example, Kumpu et al. (2012, 2013) focused on children attending daycare, whereas Morrow et al. (2010) investigated the effects of LGG in adults with ventilator-associated pneumonia. These differences in study populations may explain some of the observed heterogeneity, highlighting the need for targeted research in specific patient groups (Hojsak et al., 2010a, 2010b).

Although LGG has shown promise in respiratory disease management, it is important to consider how it compares with other probiotic strains. Several probiotics, including *L. casei*, *B. breve*, and *Lactobacillus plantarum*, have also been studied for their effects on respiratory health. For example, *L. casei* has been shown to reduce the incidence of upper respiratory tract infections in children, whereas *B. breve* has demonstrated anti-inflammatory effects in animal models of asthma (Han et al., 2021; Du et al., 2022). However, LGG stands out because of its well-documented safety profile, ability to survive the stomach's acidic environment, and strong adherence to intestinal epithelial cells, which may enhance its immunomodulatory effects (Ouweland et al., 2016).

Despite these advantages, the efficacy of LGG may vary depending on the specific respiratory condition and patient population. For example, Bruzzese et al. (2018) found no significant benefit of LGG in reducing pulmo-

nary exacerbations in children with cystic fibrosis, suggesting that LGG may not be equally effective across all respiratory diseases. This finding underscores the importance of tailoring probiotic interventions to specific conditions and patient needs (Tapiovaara et al., 2016).

This study has several limitations that should be acknowledged. First, the small number of included studies ($n=13$) and the variability in study designs may limit the findings' generalizability. Second, some studies had a high or unclear risk of bias, particularly in the blinding of outcome assessments, which could influence the results. Third, secondary outcomes (e.g., pulmonary function tests) were not included in the meta-analysis because of insufficient data, which may provide additional insights into the mechanisms underlying the effects of LGG. Finally, the results should be interpreted with caution because of the heterogeneity observed in the analysis. Moreover, further research is needed to confirm these findings.

To build on the findings of this study, future research should focus on several key areas. First, large-scale RCTs with standardized dosages, intervention durations, and outcome measures are needed to reduce heterogeneity and provide more robust evidence. Second, studies should explore the potential benefits of combining LGG with other probiotic strains or prebiotics to enhance its efficacy. For example, the coadministration of LGG with *Bifidobacterium lactis* has been shown to improve the immune responses in children with respiratory infections. Third, mechanistic studies are needed to better understand how LGG modulates respiratory immunity, particularly through the gut-lung axis. Finally, studies should investigate the long-term effects of LGG supplementation, particularly in high-risk populations, to determine its potential as a sustainable preventive strategy.

In conclusion, this systematic review and meta-analysis provide evidence that LGG effectively reduces the incidence and severity of respiratory diseases, both as a preventive and therapeutic intervention. Although the observed effect size was modest, the clinical significance of these findings should not be overlooked, particularly in high-risk populations. Nevertheless, the considerable heterogeneity among studies and the limitations of the current evidence base highlight the need for further research to optimize the use of LGG in respiratory disease management. Future studies can provide more definitive recommendations for the integration of LGG into clinical practice by addressing these gaps, ultimately improving outcomes for patients with respiratory diseases.

FUNDING

None.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: MNZ, EPW. Analysis and interpretation: MNZ. Data collection: IM, MF. Writing the article: MNZ. Critical revision of the article: MH, ID, AB. Final approval of the article: All authors. Statistical analysis: MNZ, EPW. Obtained funding: EPW. Overall responsibility: EPW.

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