Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5fo01780g

The effects of *Lacticaseibacillus rhamnosus* GG supplementation on gastrointestinal and respiratory outcomes: a systematic review and meta-analysis of randomized controlled trials†

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Lacticaseibacillus rhamnosus GG (LGG) supplementation has demonstrated efficacy in reducing diarrhea duration in children. However, its preventive potential and broader therapeutic applications beyond pediatric diarrhea remain less well characterized. A systematic review and meta-analysis were performed to investigate the efficacy of LGG supplementation on the risks of composite (including infections and symptoms) gastrointestinal (GI) and respiratory outcomes, as well as the duration of relevant symptoms. The protocol was pre-registered in the PROSPERO database (CRD42024539944). The PubMed, Web of Science, and Cochrane databases were searched for relevant articles. A random-effects model was applied to generate pooled relative risks (RRs) or weighted mean difference (WMD) estimates with 95% confidence intervals (CIs). Sixty-nine trials were included. LGG supplementation reduced the risk of composite GI outcomes (RR 0.88, 95% CI 0.81, 0.96; *N* = 38), primarily through a reduction in diarrhea risk (RR 0.64, 95% CI 0.52, 0.77; *N* = 24) and, to a lesser extent, taste disturbances (RR 0.40, 95% CI 0.22, 0.72; *N* = 5). Other GI outcomes—including vomiting (*N* = 13), nausea (*N* = 9), abdominal pain (*N* = 12), bloating (*N* = 8), constipation (*N* = 8), stomach rumbling (*N* = 3), and loss of appetite (*N* = 5)—showed limited effect. Respiratory outcome risk was also lower (RR 0.86, 95% CI 0.78, 0.94; *N* = 23), largely attributable to reduced respiratory infection risk (RR 0.87, 95% CI 0.79, 0.97; *N* = 18), with limited effects on respiratory symptom risk (*N* = 7). LGG supplementation shortened GI symptom duration (WMD −0.62, 95% CI −0.81, −0.44 days; *N* = 33), largely attributable to reduced diarrhea duration (−0.83, 95% CI −1.06, −0.59 days; *N* = 29), with limited effects on vomiting duration (*N* = 6). LGG had limited effects on respiratory symptoms (*N* = 6). Moderate-to-high heterogeneity was observed for the aforementioned outcomes, except GI outcomes other than diarrhea and GI symptom risk. Prediction intervals supported consistent benefits for diarrhea outcomes but frequently crossed the null for others, indicating greater uncertainty. Effects on diarrhea outcomes and respiratory infection risk were more consistent in children; evidence in adults was limited. Certainty was rated moderate for diarrhea outcomes and mostly low for others. LGG supplementation reduces diarrhea risk and duration in children, supported by moderate-certainty evidence and consistent effects across trials. Other outcomes showed more variable results, reflecting limited or inconsistent evidence. These findings support LGG's role in pediatric diarrhea management and prevention while underscoring the need for high-quality trials to clarify broader clinical applications.

Received 16th April 2025,
Accepted 13th June 2025

DOI: 10.1039/d5fo01780g

rsc.li/food-function

Introduction

Probiotics are living microorganisms that confer health benefits to the host when administered adequately.[1] In addition to their established roles in gastrointestinal (GI) health, some strains exhibit systemic effects, including immunomodulatory and anti-inflammatory properties relevant to various medical conditions.[2,3] Among the most extensively studied probiotics are members of the *Lactobacillaceae* family —rod-shaped, Gram-positive, non-spore-forming bacteria that

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d5fo01780g

are typically facultative anaerobes. In humans, *Lactobacillaceae* naturally inhabit the GI and female genital tracts. One of the most prominent strains within this family is *Lacticaseibacillus rhamnosus* GG (formerly *Lactobacillus rhamnosus* GG, or LGG), first isolated from the fecal samples of healthy human volunteers by researchers Sherwood Gorbach and Barry Goldin, whose initials form the "GG" designation. LGG is distinguished by its remarkable resilience in acidic and bile-rich environments, vigorous growth, and strong adhesive properties that facilitate its attachment to the intestinal epithelium.[4,5] Since its discovery, LGG has been widely investigated for its potential to support various aspects of human health, including GI and respiratory conditions.[4]

LGG is well-known for its effectiveness in managing pediatric diarrhea, with multiple meta-analyses of randomized controlled trials (RCTs) consistently demonstrating its ability to reduce diarrhea duration in children.[6–8] However, these meta-analyses have largely focused on therapeutic applications, with limited attention to preventive outcomes or GI conditions beyond pediatric diarrhea. A broader evaluation that includes preventive endpoints and diverse GI conditions is necessary to clarify the potential of LGG in maintaining GI health.

Beyond the GI tract, emerging evidence implicates gut microbiota in shaping respiratory health through the gut–lung axis—a bidirectional communication pathway between the gut microbiota and respiratory tract mediated by immune signaling and microbiota-derived metabolites such as short-chain fatty acids (SCFAs).[9–12] SCFAs, produced through microbial fermentation of dietary fibers in the colon, can enter systemic circulation and have been reported to modulate immune cell differentiation, attenuate inflammatory signaling, and limit pulmonary infiltration of immune cells.[9–12] These mechanisms support the hypothesis that gut microbial activity may exert immunomodulatory effects at distal sites, including the respiratory tract. Given these shared immune pathways, evaluating both GI and respiratory outcomes may offer a broader understanding of the effects of LGG supplementation. This perspective is consistent with growing interest in the gut–lung axis as a conceptual model for investigating host–microbiota interactions across organ systems. Although a previous meta-analysis reported potential benefits of LGG in preventing respiratory infections, its findings were based on a small number of trials (N = 4).[13] Since then, additional RCTs have been conducted, permitting a more comprehensive synthesis of the current evidence.

Evaluating both GI and respiratory outcomes within a single analytical framework is supported by shared microbial and immune-related mechanisms, particularly those involving systemic immune modulation and microbiota-derived metabolites. A unified meta-analysis enables a more integrated understanding of the potential multisystem effects of LGG, while maintaining separate outcome analyses for clinical relevance. Although LGG is well-established in the management of pediatric diarrhea, and evidence is growing for its potential in respiratory health, no meta-analysis has yet examined its preventive and therapeutic effects across both domains using a comprehensive and updated set of trials. The present meta-analysis was conducted to address that gap by systematically synthesizing RCTs with two primary objectives: (1) to evaluate the preventive efficacy of LGG in reducing the incidence of GI and respiratory conditions, and (2) to assess its therapeutic efficacy in reducing the duration of GI and respiratory symptoms. By incorporating recent trials and broadening the analytic scope beyond prior reviews, this work offers a more complete assessment of the potential clinical applications of LGG in GI and respiratory health.

Methods

The present systematic review and meta-analysis was prepared and reported according to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement.[14] The research question was constructed using the Participants, Interventions, Comparisons, Outcomes, and Study (PICOS) framework. The protocol of the present systematic review and meta-analysis was pre-registered in the PROSPERO database (**https://www.crd.york.ac.uk/PROSPERO/**; registration no. CRD42024539944). Two investigators (K.H. and L.Z.) independently conducted the literature search, study selection, data extraction, and assessments of the risk of bias (RoB) and the certainty of the evidence. Disagreements between the investigators were resolved by consensus.

Literature search

The PubMed, Web of Science, and Cochrane databases were searched for relevant articles from inception to May 2024. The full details of the search strategy are summarized in ESI Table 1.†

Study selection

The inclusion and exclusion criteria according to the PICOS framework are shown in Table 1. Briefly, RCTs that enrolled children (<18 years) or adults (≥18 years) were included in the present meta-analysis if they met all the following inclusion criteria: (1) one or more intervention groups received LGG supplementation and were compared with LGG-free control or placebo. (2) Reported effects on the risk of respiratory symptoms or infections, the risk of gastrointestinal (GI) symptoms or infections, gastrointestinal symptom duration, or respiratory symptom duration. As pre-specified in the PROSPERO registration, the primary outcomes were: (I) composite respiratory outcomes, defined as the occurrence of respiratory tract infections or respiratory symptoms. (II) Composite gastrointestinal outcomes, defined as the occurrence of GI infections or GI symptoms.

Respiratory tract infections included upper respiratory tract infections (rhinitis, pharyngitis, sinusitis, otitis, or the common cold) and lower respiratory tract infections (pneumonia, tracheobronchitis, bronchitis, or bronchiolitis). Respiratory symptoms included one or more of: fever, chills, runny nose (rhinorrhea), nasal congestion, sore throat (phar-

Table 1 Participants, interventions, comparisons, outcomes, and study (PICOS) design framework

	Inclusion criteria	Exclusion criteria
Participants	Humans (children (<18 years) and adults (≥18 years))	Animals
Intervention or exposure	Direct *Lacticaseibacillus rhamnosus* GG intervention	Indirect *Lacticaseibacillus rhamnosus* GG intervention (pre-natal (in-utero) or *via* lactating mother) Mixture of *Lacticaseibacillus rhamnosus* GG and other probiotics
Comparison	*Lacticaseibacillus rhamnosus* GG-free control or placebo	*Lacticaseibacillus rhamnosus* GG-containing placebo or control
Outcome	Primary: composite gastrointestinal outcomes (including gastrointestinal symptoms and infections) and composite respiratory outcomes (including respiratory symptoms and infections) Secondary: gastrointestinal symptom duration and respiratory symptom duration	
Study design	Parallel or cross-over randomized controlled trial	Non-randomized study (*i.e.*, observational study)

yngitis), cough, sneezing, wheezing, muscle pain (myalgia), or earache.

GI infections were defined as diarrhea with more than three loose or watery stools within 24 hours, with or without vomiting, or laboratory-confirmed viral or bacterial GI infection. Gastrointestinal symptoms included one or more of the following: diarrhea, abdominal pain, vomiting, nausea, bloating, constipation, flatulence, taste disturbance, or loss of appetite.

Although composite outcomes vary across clinical fields, the rationale for the current definitions reflects the frequent overlap between symptom-based and diagnostic endpoints in LGG trials. Since trials often report these elements inconsistently, combining symptoms and infections into a composite outcome maximized data inclusion while maintaining clinical relevance. To allow accurate interpretation of the intervention's efficacy and mitigate concerns about heterogeneity, stratification by major subtypes was conducted to determine whether LGG effects differed by outcome subtype.

The secondary outcomes were the duration of any GI or respiratory symptoms. All outcomes were pre-defined and registered in advance.

If multiple doses of LGG were assigned, the one with the highest dose was included. In cases where LGG was administered alone or alongside other agents, LGG was chosen instead of LGG plus another agent to isolate its effects. If LGG was given in combination with multiple doses of other agents, the lowest dose of other agents was included to minimize the potential biasing effect of other agents. When different publications from the same trial were identified, the one with the largest sample size, longest duration, or most comprehensive data was selected. If both the original trial and a follow-up study reported outcomes, only the original trial was included to avoid potential bias due to loss to follow-up. However, if the original trial was unavailable, the follow-up study was included.

Data extraction

The following information was recorded from each RCT using standardized forms: first author name; year of publication; participant characteristics including mean age, sex, and relevant participant descriptions; trial characteristics including trial design, intervention duration, comparison; number of participants in the LGG or control groups; number of participants who developed GI and respiratory symptoms during the intervention; daily dose of LGG; risk estimates for composite GI and respiratory outcomes; and mean duration of GI and respiratory symptoms before and after LGG supplementation.

Assessments of RoB and the certainty of evidence

RoB in the included RCTs was assessed using the Cochrane Collaboration tool,[15] which covers six domains (each domain comprises one or more items): selection bias (random sequence generation; allocation concealment), performance bias (blinding of the participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. Each domain was rated as low, high, or unclear risk of bias.

The certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach.[16] This approach evaluates five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. All outcomes started at high certainty, as they were based on RCTs, and were downgraded by one or two levels if serious or very serious concerns were identified in any of the five domains. The overall certainty for each outcome was rated as high, moderate, low, or very low.

Statistical analyses

The relative risk (RR) was used as the summary measure for assessing the risks of composite GI and respiratory outcomes. If the relative risk (RR) was not directly reported, RR was calculated using the number of participants in the LGG and control groups and those who developed the outcomes in each group or by converting other risk estimates, such as the odds ratio.[17]

The weighted mean difference (WMD) was employed to summarize effect sizes for the duration of GI and respiratory symptoms. To estimate the effect size for outcome duration, the mean difference, standard deviation, and sample size from

each RCT were required. If the standard deviation was not reported, it was derived from the standard error, CI, or *P*-value using standard formulas.[18]

A random-effects model was applied to generate pooled RRs or WMDs with 95% confidence intervals (CIs).[19] Heterogeneity across RCTs was assessed using the I^2 statistic (heterogeneity: <25% low, 25–50% moderate, >50% high).[20] To explore sources of heterogeneity and potential effect modifiers, subgroup and meta-regression analyses were conducted according to age group, intervention duration, daily dose of LGG, sample size, geographic region, and outcome subtypes. For diarrhea duration, additional variables (*i.e.*, pre-trial diarrhea duration, diarrhea etiology, and rotavirus positive proportion) were also examined in the subgroup and meta-regression analysis. As an alternative solution to appraising heterogeneity, the prediction interval (PI) was calculated to estimate the range within which the true effects of future studies would be expected to fall, accounting for between-study variability. Sensitivity analysis was conducted by excluding antibiotic-related events and restricting the analysis to either adults or children.

Publication bias was evaluated through funnel plot inspection and using Begg's rank correlation test and Egger's linear regression,[21] and if bias was detected, the trim-and-fill method was applied to adjust for it.[22] In accordance with guidance from the Cochrane Handbook (Chapters 9.6.5.1 and 10.4.5),[23] subgroup analyses, meta-regressions, and statistical tests for small-study effects were only performed when at least 10 RCTs were available. This threshold reflects widely accepted practice to ensure sufficient power and reliability in these exploratory analyses. As noted in the Handbook, ten studies per covariate are typically recommended for meta-regression, and fewer than ten studies may yield unreliable results due to uneven covariate distribution. Similarly, tests for funnel plot asymmetry require a minimum of ten studies due to low power and potential distortions in smaller samples. While this may limit the number of eligible comparisons, this threshold was applied consistently to avoid overinterpreting underpowered findings. All statistical analyses were performed using STATA software, version 11.0 (StataCorp., College Station, TX, USA). All *P* values were two-sided, and the significance level was <0.05.

Results

Literature search

The study selection process and the reasons for exclusion are presented in ESI Fig. 1.† After removing duplicates and screening titles and abstracts, 150 articles were selected for full-text review. Of these, 81 articles were excluded for various reasons (reported in the ESI, pages 1–6†). Sixty-nine articles published between 1990 and 2024 were included in the meta-analysis.[24–92]

Gastrointestinal outcomes

Sixty-two RCTs were available for GI outcomes,[24–85] with their characteristics summarized in ESI Table 2 and detailed in the ESI (pages 7†). The RoB assessment is reported in ESI Table 3 and detailed in the ESI (page 7).†

Primary outcomes: LGG and the risk of GI outcomes

Main analysis and prediction interval. Thirty-eight RCTs, with 4775 participants in the LGG group and 4732 in the control group, were included in the analysis of composite GI outcomes.[24–61] LGG supplementation reduced the risk of composite GI outcomes (RR 0.88, 95% CI 0.81, 0.96; Fig. 1A), with moderate heterogeneity (I^2 = 47%).

The outcomes of interest can be further categorized into several specific GI conditions, including diarrhea,[24–28,30–32,37,40–44,46,49–53,56,57,59,61] taste disturbance,[28,32,41,49,61] vomiting,[28,32,35–37,41–43,51,53,56,57,60] nausea,[28,32,36,37,41,46,52,56,61] abdominal pain,[28,32,35,36,41,46,49,50,52,57,60,61] bloating,[28,32,46,49,50,52,56,61] constipation,[28,32,41,46,52,56,57,61] stomach rumbling,[46,52,56] and loss of appetite.[28,32,41,46,58] Reductions in risk with LGG supplementation were observed for diarrhea (RR 0.64, 95% CI 0.52, 0.77; Fig. 1B) and taste disturbance (RR 0.40, 95% CI 0.22, 0.72), but not for vomiting, nausea, abdominal pain, bloating, constipation, stomach rumbling, and loss of appetite (ESI Fig. 2†).

The PIs provide insight into the expected range of effects in future trials, reflecting heterogeneity across trials. For the composite gastrointestinal (GI) outcome, the PI (0.67, 1.16) includes the null value, suggesting that although the pooled estimate indicates a significant reduction in risk with LGG supplementation, future trials may yield mixed results. Diarrhea (PI: 0.52, 0.77) and taste disturbance (PI: 0.16, 0.96) showed significant pooled effects and PIs excluding 1, supporting consistent benefit across trials. In contrast, wide PIs for vomiting (0.32, 2.13), bloating (0.23, 2.32), and loss of appetite (0.91, 2.09) reflect substantial variability and uncertainty in future effect estimates. The PIs for nausea (0.63, 1.34), abdominal pain (0.88, 1.10), constipation (0.70, 1.56), and stomach rumbling (0.56, 1.49) also include the null, indicating that future trials may not consistently demonstrate benefit. Overall, while LGG appears robustly effective for reducing diarrhea and possibly taste disturbance, its effects on other GI symptoms remain uncertain across varied populations and settings.

Publication bias

Visual inspection of the funnel plots revealed distinct distribution patterns across outcomes. For composite GI symptoms, smaller or less precise trials (right side) with $\ln RR > 0$ were notably sparse, whereas larger or more precise studies clustered near $\ln RR \approx -1$. The diarrhea plot showed a milder version of this pattern, with fewer larger or more precise trials in the $\ln RR > 0$ range. In contrast, the vomiting plot appeared symmetric, with studies evenly distributed across log RR ($\ln RR$) values at all levels of precision. For abdominal pain, larger or more precise studies clustered tightly near $\ln RR \approx -1$, accompanied by a few scattered smaller or less precise trials. These visual patterns were supported by statistical tests,

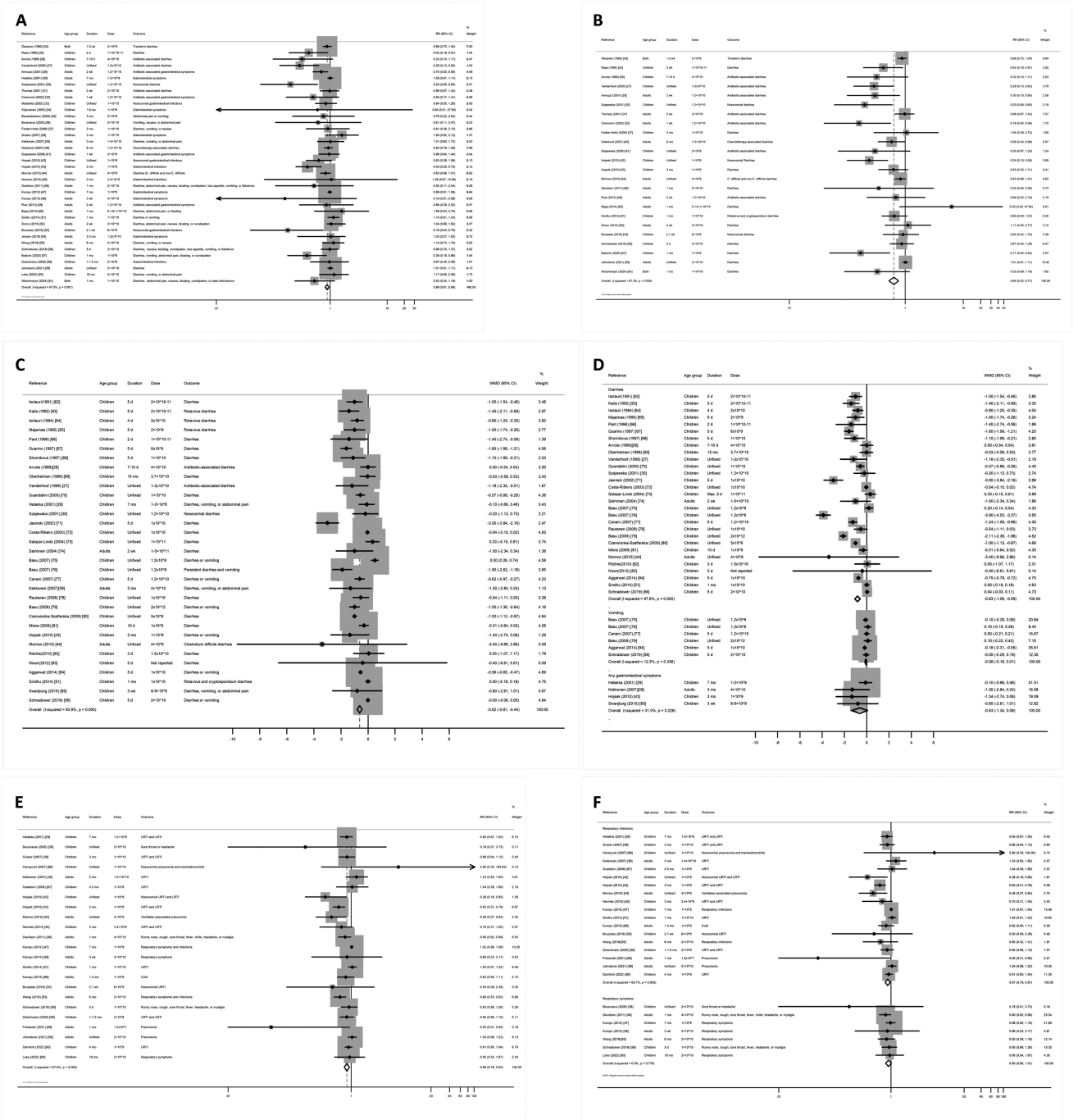

Fig. 1 The effects of *Lacticaseibacillus rhamnosus* GG supplementation on the risk and duration of gastrointestinal and respiratory outcomes. (A) The effect of *Lacticaseibacillus rhamnosus* GG supplementation on the risk of composite gastrointestinal outcomes. (B) The effect of *Lacticaseibacillus rhamnosus* GG supplementation on the risk of diarrhea. (C) The effect of *Lacticaseibacillus rhamnosus* GG supplementation on the duration of gastrointestinal symptoms. (D) The effects of *Lacticaseibacillus rhamnosus* GG supplementation on the duration of diarrhea, vomiting, and any gastrointestinal symptoms. (E) The effect of *Lacticaseibacillus rhamnosus* GG supplementation on the risk of composite respiratory outcomes. (F) The effects of *Lacticaseibacillus rhamnosus* GG supplementation on the risk of respiratory infections and symptoms. LRTI: lower respiratory tract infection, URTI: upper respiratory tract infection.

which indicated publication bias for composite GI outcomes (Begg's $P = 0.04$; Egger's $P < 0.01$) and diarrhea (Begg's $P = 0.18$; Egger's $P < 0.01$), but not for vomiting (Begg's $P = 0.73$; Egger's $P = 0.17$) or abdominal pain (Begg's $P = 0.94$; Egger's $P = 0.18$). However, the trim-and-fill method did not identify any missing studies, and the pooled RRs remained unchanged.

Subgroup, meta-regression, and sensitivity analyses

Subgroup and meta-regression analyses were conducted to assess the risks of composite GI outcomes, diarrhea, vomiting, and abdominal pain. No significant effect of LGG supplementation on vomiting and abdominal pain was identified across subgroups. A tendency toward risk reduction for composite GI outcomes and diarrhea with LGG supplementation was observed across subgroups, although this effect did not consistently reach statistical significance (Table 2). Meta-regression analyses did not reveal any significant impact of the examined variables on the overall intervention effect (P for meta-regression $\geq$0.05; Table 2). Low heterogeneity was observed in trials involving adults (I^2 = 0%) and those administering higher doses of LGG (I^2 = 23.4%) for composite GI outcomes and few Asian trials for diarrhea (Table 2).

When antibiotic-related events were excluded, and the analyses were restricted to either children or adults, a significant reduction in the risks of GI outcome and diarrhea was more consistently observed across subgroups in children. In contrast, no such benefits were seen in adults. For pediatric diarrhea, benefits were evident in nearly all subgroups, except in trials using multiple doses (ESI Table 4†).

Certainty of the evidence

The certainty of the evidence was graded as moderate for the risks of diarrhea, vomiting, and abdominal pain, and low for all other outcomes (ESI Table 5†). Most outcomes were downgraded due to imprecision and suspected publication bias. Vomiting and abdominal pain appeared relatively free from publication bias based on visual inspection and statistical tests, while composite GI outcomes and diarrhea showed signs of publication bias. Other outcomes were not assessed for publication bias due to the limited number of trials and were therefore downgraded despite the lack of direct evidence of bias. Although diarrhea exhibited high heterogeneity, the evidence was not downgraded for inconsistency, as the prediction interval supported a consistent benefit across future trials, suggesting that inconsistency is unlikely to undermine the reliability of this finding.

Table 2 Subgroup and meta-regression analyses of the effects of *Lacticaseibacillus rhamnosus* GG supplementation on the risks of composite gastrointestinal outcomes and diarrhea

	Composite gastrointestinal outcomes				Diarrhea			
	Trials (participants/cases)	RR (95% CI)	I^2 (%)	P*	Trials (participants/cases)	RR (95% CI)	I^2 (%)	P*
Overall	38 (9507/4084)	**0.88 (0.81, 0.96)**	47	—	24 (7325/2717)	**0.64 (0.52, 0.77)**	67.3	—
Age group								
Children (<18 years)	21 (4091/1076)	**0.75 (0.62, 0.91)**	62.2		12 (2876/344)	**0.47 (0.34, 0.66)**	51.5	
Adults (≥18 years)	15 (4478/2654)	0.97 (0.91, 1.02)	0	0.17[c]	10 (3511/2030)	0.80 (0.63, 1.03)	60.6	0.09[c]
Both	2 (938/354)	0.80 (0.54, 1.18)	32.4	0.91[c]	2 (938/343)	0.67 (0.28, 1.59)	54.5	0.36[c]
Intervention duration[a]								
Longer	11 (2256/1162)	0.97 (0.87, 1.07)	34.6		8 (1012/237)	**0.58 (0.39, 0.88)**	38.2	
Shorter	20 (3157/927)	**0.84(0.72, 0.97)**	35.7	0.99[d]	10 (2447/571)	**0.73 (0.56, 0.95)**	46.5	0.12[d]
Unfixed	7 (4094/1995)	**0.72 (0.54, 0.94)**	72.5	0.15[d]	6 (3866/1909)	**0.53 (0.35, 0.79)**	84.6	0.60[d]
Daily dose								
≥1 × 10^{10} CFU	25 (6115/2619)	0.90 (0.79, 1.02)	56.6	0.45	17 (5151/2153)	**0.61 (0.46, 0.80)**	66.9	0.91
<1 × 10^{10} CFU	13 (3392/1465)	**0.85 (0.75, 0.96)**	42.9		7 (2174/564)	**0.64 (0.47, 0.87)**	68.7	
Dose frequency								
Single dose	17 (6542/3365)	**0.89 (0.81, 0.99)**	60.5	0.87	10 (5057/2324)	**0.60 (0.45, 0.81)**	79.5	0.88
Multiple doses	21 (2965/719)	**0.87 (0.75, 0.99)**	23.4		14 (2268/393)	**0.65 (0.50, 0.86)**	44.1	
Sample size								
≥120	18 (8279/3796)	**0.91 (0.84, 0.99)**	55.3	0.32	12 (6546/2551)	**0.72 (0.60, 0.87)**	70.1	0.34
<120	20 (1228/288)	**0.72 (0.55, 0.95)**	34.7		12 (779/166)	**0.50 (0.30, 0.81)**	52.3	
Region[b]								
Europe	23 (4397/1738)	**0.83 (0.74, 0.94)**	51.8		13 (2659/627)	**0.48 (0.33, 0.69)**	67.3	
North America	11 (4734/2194)	0.92 (0.79, 1.07)	39.5	0.43[e]	8 (4452/2020)	0.84 (0.66, 1.06)	62.8	0.12[e]
Asia	2 (155/105)	0.74 (0.28, 1.96)	82.7	0.69[e]	2 (155/60)	**0.57 (0.38, 0.87)**	0	0.81[e]
Oceania	1 (162/36)	Not pooled	—		0	—	—	
South America	1 (59/11)	Not pooled	—		1 (59/10)	Not pooled	—	
Outcome subtypes								
Antibiotic-associated	8 (3512/1820)	0.77 (0.59, 1.01)	64.7	0.42[f]	8 (3515/1738)	**0.51 (0.32, 0.82)**	75.5	0.32[f]
Nosocomial	4 (1133/152)	**0.49 (0.26, 0.91)**	64.1	0.05[f]	3 (913/73)	0.37 (0.14, 1.03)	75.8	0.13[f]
Unspecified or other	27 (7512/3684)	0.95 (0.88, 1.02)	29.6		14 (5550/2478)	**0.78 (0.66, 0.93)**	56.1	

Bold numbers indicate statistically significant $P < 0.05$. CI confidence interval; RR relative risk. *P value for heterogeneity of intervention effect between subgroups according to meta-regression analysis. [a] Longer duration corresponds to ≥3 months for composite gastrointestinal outcomes and ≥1 month for diarrhea. Shorter duration corresponds to <3 months for composite gastrointestinal outcomes and <1 month for diarrhea. [b] Although the trial by Johnstone *et al.* enrolled participants from the United States, Canada, and Saudi Arabia, it was classified as North American due to the majority of participants being from the United States and Canada. [c] Trials enrolling children as a reference group. [d] Trials with longer duration as a reference group. [e] Trials conducted in Europe as a reference group. [f] Trials on unspecified or other outcome as a reference group.

Secondary outcomes: LGG and GI symptom duration

Main analysis. Thirty-three RCTs, with 2941 in the LGG group and 2939 in the control group, were included in the analysis of GI symptom duration.[26,27,29,30,39,43,44,51,56,62–85] LGG supplementation reduced GI symptom duration (−0.62, 95% CI −0.81, −0.44 days; Fig. 1C), with high heterogeneity (I^2 = 93.9%).

The outcome can be further stratified into several types, namely diarrhea,[26,27,30,44,51,56,62–84] vomiting,[56,75–77,79,84] and any other GI symptoms.[29,39,43,85] LGG supplementation reduced diarrhea duration (−0.83, 95% CI −1.06, −0.59 days) but not the duration of any other GI symptoms (Fig. 1D). Heterogeneity was high for diarrhea (I^2 = 97.6%) and moderate or low for any other GI symptoms.

While the pooled estimate indicated that LGG supplementation significantly reduced GI symptom duration, the corresponding PI (−1.5, 0.27) included the null, suggesting uncertainty regarding whether this benefit would be observed consistently in future trials. For diarrhea duration, both the pooled estimate and the PI (−1.07, −0.58) excluded the null, indicating a consistent reduction across trials. In contrast, vomiting duration was not significantly reduced in the pooled analysis, and the PI (−0.20, 0.05) similarly included the null, reinforcing the uncertainty regarding any benefit of LGG for this outcome.

Publication bias

Visual inspection of the funnel plots revealed that most effect sizes clustered around WMD values of 0 to −1 day, with larger or more precise trials (top of the funnel) showing consistent, modest reductions in symptom duration. Both plots appeared asymmetric, with smaller or less precise trials (bottom of the funnel) disproportionately absent on the right side, where null or unfavorable effects would be expected. Statistical tests supported these observations: for GI symptoms, both Begg's and Egger's tests indicated significant asymmetry (P < 0.01), while for diarrhea, only Egger's test was significant (P < 0.01). However, the trim-and-fill analysis did not identify any missing studies, and the pooled estimates remained unchanged.

Subgroup, meta-regression, and sensitivity analyses

A trend toward the shortened duration of composite GI outcomes and diarrhea was observed across subgroups, although statistical significance was not always achieved (Table 3). Low heterogeneity was observed in trials in adults (I^2 = 0%) and those with longer intervention durations for GI symptom duration ($I^2 \leq$ 24.6%) for both outcomes, and those investigating *Clostridioides difficile*-induced diarrhea for diarrhea duration (Table 3). A more pronounced reduction in diarrhea duration was observed among participants with a pre-trial diarrhea duration of ≥14 days compared to those with ≤7 days (P meta-regression = 0.01) or with unknown pre-trial duration (P meta-regression = 0.04). Additionally, the reduction was greater for *Clostridioides difficile*-induced diarrhea than for rotavirus-caused diarrhea (P meta-regression = 0.04). Excluding all antibiotic-related events and restricting the analyses to children yielded results comparable to the original findings (ESI Table 6†).

Certainty of the evidence

The certainty of the evidence was graded as moderate for diarrhea duration and low for all outcomes (ESI Table 5†). GI symptom duration and diarrhea duration were downgraded due to indications of publication bias based on visual inspection and statistical tests. While both outcomes showed high heterogeneity, only GI symptom duration was downgraded for inconsistency, as the prediction interval for diarrhea duration—but not for GI symptom duration—supported a consistent reduction across future trials. Vomiting duration was downgraded due to imprecision and was not assessed for publication bias due to the limited number of trials, and was therefore downgraded despite the absence of direct evidence of bias.

Respiratory outcomes

Twenty-six RCTs were included in the analysis of respiratory outcomes,[29,36,38,39,42–48,51,53,55,56,58–60,85–92] with their characteristics summarized in ESI Table 7 and detailed in the ESI (page 7†). The RoB assessment is reported in ESI Table 8 and detailed in the ESi (pages 8†).

Primary outcomes: LGG and the risk of composite respiratory outcomes

Main analysis. Twenty-three RCTs, with 3546 in the LGG group and 3573 in the control group, were included in the analysis of composite respiratory outcomes.[29,36,38,39,42–48,51,53,55,56,58–60,86–90] LGG supplementation significantly reduced the risk of composite respiratory outcomes (RR 0.86, 95% CI 0.78, 0.94; Fig. 1E), with high heterogeneity (I^2 = 67%).

The outcomes of interest can be further categorized into two broad groups: respiratory infections,[29,38,39,42–45,47,51,53,55,58,59,86–90] and symptoms.[36,46–48,55,56,60] LGG supplementation significantly reduced the risk of respiratory infections (RR 0.87, 95% CI 0.79, 0.97) but not respiratory symptoms (RR 0.90, 95% CI 0.80, 1.01) (Fig. 1F). Heterogeneity was high for respiratory infections (I^2 = 65.7%) and low for respiratory symptoms (I^2 = 0%). Stratification by infection site showed significant effects only when upper and lower respiratory tract infections were analyzed together, but not separately (Table 4).

Despite significant pooled reductions in risks for composite respiratory outcomes and respiratory infections, the corresponding PIs (0.62, 1.18 and 0.65, 1.18, respectively) included the null, suggesting inconsistent effects across trials. For respiratory symptoms, both the pooled estimate and the PI (0.80, 1.01) included the null, indicating uncertainty regarding any benefit of LGG for this outcome.

Publication bias

Funnel plot asymmetry was most pronounced for composite respiratory outcomes, where small or imprecise studies with unfavorable effects appeared underrepresented. The plot for respiratory infections showed milder, yet still visible, asymmetry, with fewer small or imprecise studies reporting unfavor-

Table 3 Subgroup and meta-regression analyses of the effect of *Lacticaseibacillus rhamnosus* GG supplementation on the duration of gastrointestinal symptoms and diarrhea

	Gastrointestinal symptoms				Diarrhea			
	Trials (participants)	WMD (95% CI), days	I^2 (%)	P*	Trials (participants)	WMD (95% CI), days	I^2 (%)	P*
Overall	33 (5880)	**−0.62 (−0.81, −0.44)**	93.9	—	29 (4935)	**−0.83 (−1.06, −0.59)**	97.6	—
Age group								
Children (<18 years)	30 (5710)	**−0.61 (−0.79, −0.42)**	94.4	0.40	27 (4884)	**−0.82 (−1.06, −0.58)**	97.7	0.71
Adults (≥18 years)	3 (170)	**−1.19 (−2.19, −0.19)**	0		2 (51)	−1.11 (−2.42, 0.21)	0	
Intervention duration								
≥1 week	9 (1636)	−0.17 (−0.37, 0.04)	24.6		4 (481)	−0.02 (−0.18, 0.14)	0	
<1 week	13 (2033)	**−0.97 (−1.32, −0.63)**	95.1	0.05[b]	14 (2243)	**−0.99 (−1.33, −0.64)**	97.3	0.07[b]
Unfixed	11 (2211)	**−0.53 (−0.94, −0.11)**	96.2	0.57[b]	11 (2211)	**−0.91 (−1.48, −0.33)**	98.1	0.31[b]
Daily dose								
≥1 × 10^{10} CFU	22 (3587)	**−0.53 (−0.71, −0.35)**	91.5		21 (1338)	**−0.70 (−0.97, −0.44)**	97.8	
<1 × 10^{10} CFU	10 (2164)	**−0.82 (−1.39, −0.24)**	94.3	0.57	7 (3468)	**−1.26 (−2.02, −0.51)**	96.1	0.24
Not reported	1 (129)	Not pooled	—	—	1 (129)	Not pooled	—	—
Dose frequency								
Single dose	14 (2420)	**−0.63 (−0.93, −0.33)**	95.2		11 (1594)	**−0.68 (−1.01, −0.35)**	98	
Multiple doses	18 (3331)	**−0.65 (−0.99, −0.32)**	91.5	0.89	17 (3212)	**−0.91 (−1.46, −0.37)**	97	0.74
Not reported	1 (129)	Not pooled	—	—	1 (129)	Not pooled	—	—
Sample size								
≥120	17 (4787)	**−0.89 (−1.23, −0.55)**	82.2	0.11	14 (3976)	**−0.89 (−1.25, −0.53)**	83.4	0.81
<120	16 (1093)	**−0.37 (−0.55, −0.18)**	92.5		15 (959)	**−0.77 (−1.10, −0.45)**	98.7	
Region								
Europe	17 (2199)	**−0.80 (−1.02, −0.58)**	65.9		13 (1254)	**−0.90 (−1.13, −0.67)**	68.5	
Asia	7 (1812)	**−0.53 (−0.96, −0.10)**	94.7	0.30[c]	7 (1812)	**−1.12 (−1.73, −0.50)**	98.1	0.58[c]
North America	4 (1277)	−0.45 (−1.36, 0.46)	39.9	0.19[c]	4 (1277)	−0.45 (−1.42, 0.52)	43.6	0.11[c]
South America	4 (528)	−0.59 (−1.45, 0.27)	94	0.51[c]	4 (528)	−0.59 (−1.45, 0.27)	94	0.47[c]
Oceania	1 (64)	Not pooled	—	—	1 (64)	Not pooled	—	—
Pre-trial diarrhea duration								
≥14 days	—	Not applicable	—	—	3 (295)	**−2.17 (−4.24, −0.10)**	90.8	
7 days	—	Not applicable	—	—	9 (1554)	**−0.67 (−1.10, −0.25)**	98.1	0.01[d]
≤5 days	—	Not applicable	—	—	7 (1026)	**−0.98 (−1.62, −0.34)**	96.3	0.20[d]
Not reported	—	Not applicable	—	—	9 (1979)	−0.56 (−1.15, 0.02)	96.8	0.04[d]
Free from diarrhea	—	Not applicable	—	—	1 (81)	Not pooled	—	—
Diarrhea etiology								
Rotavirus	—	Not applicable	—	—	7 (374)	**−0.98 (−1.47, −0.48)**	94.5	
Clostridioides difficile	—	Not applicable	—	—	2 (31)	**−4.58 (−7.08, −2.07)**	0	0.04[e]
Antibiotics-induced	—	Not applicable	—	—	2 (307)	−0.47 (−0.66, 1.06)	68.9	0.33[e]
Any or unknown pathogens or unspecified etiology	—	Not applicable	—	—	22 (4466)	**−0.82 (−1.08, −0.55)**	98.1	0.73[e]
Rotavirus positive proportion[a]								
100%	—	Not applicable	—	—	7 (374)	**−0.98 (−1.47, −0.48)**	94.5	
≥50% to <100%	—	Not applicable	—	—	10 (1976)	**−0.69 (−1.04, −0.34)**	98.6	0.42[f]
<50%	—	Not applicable	—	—	8 (1870)	**−0.65 (−1.12, −0.17)**	91.1	0.51[f]
None or not reported	—	Not applicable	—	—	5 (637)	−1.75 (−3.62, 0.11)	93.6	0.34[f]

Bold numbers indicate statistically significant $P < 0.05$. CI confidence interval; WMD weighted mean difference. *P value for heterogeneity of intervention effect between subgroups according to meta-regression analysis. [a] Trials on antibiotic-associated and non-infectious diarrhea were not included. [b] Trials with intervention duration of ≥1 week as a reference group. [c] Trials conducted in Europe as a reference group. [d] Pre-trials diarrhea duration of ≥14 days as a reference group. [e] Rotavirus as a reference group. [f] 100% as a reference group.

able effects than expected in a symmetrical distribution. Statistical tests supported these patterns: Begg's test did not indicate significant publication bias (composite respiratory outcomes $P = 0.77$; respiratory infections $P = 0.43$), whereas Egger's test detected publication bias in both outcomes ($P \leq 0.01$). The trim-and-fill method did not impute any missing studies, and the pooled estimates remained unchanged.

Subgroup, meta-regression, and sensitivity analysis

A trend toward reduced risks of composite respiratory outcomes and respiratory infections with LGG supplementation was noted across most subgroups, although these reductions were not always statistically significant (Table 4). Meta-regression analyses did not identify any significant effect modification by the examined variables (P for meta-regression ≥0.11; Table 4). Low heterogeneity was observed in RCTs with smaller sample sizes for composite respiratory outcomes and those administering higher doses of LGG for respiratory infections ($I^2 = 6.3\%$) (Table 4).

When events related to antibiotic use were excluded and analyses were restricted to either children or adults (ESI Table 9†), benefits were more consistently observed in children, whereas trials in adults more frequently showed no effect of LGG supplementation.

Table 4 Subgroup and meta-regression analyses on the effects of *Lacticaseibacillus rhamnosus* GG supplementation on the risks of composite respiratory outcomes and respiratory infections

	Composite respiratory outcomes				Respiratory infections			
	Trials (participants/cases)	RR (95% CI)	I^2 (%)	P*	Trials (participants/cases)	RR (95% CI)	I^2 (%)	P*
Overall	23 (7119/2660)	**0.86 (0.78, 0.94)**	67	—	18 (5864/2338)	**0.87 (0.79, 0.97)**	65.7	—
Age group								
Children (<18 years)	15(4449/1747)	**0.88 (0.79, 0.98)**	60.6	0.62	12 (3261/1557)	**0.87 (0.78, 0.98)**	66.2	0.97
Adults (≥18 years)	8 (2670/913)	0.80 (0.64, 1.01)	71.5		6 (2603/781)	0.81 (0.58, 1.11)	70.2	
Intervention duration								
≥3 months	10 (2685/1589)	**0.86 (0.74, 0.99)**	76.5		9 (2523/1457)	**0.87 (0.77, 0.99)**	68.2	
<3 months	8 (1369/386)	0.88 (0.75, 1.03)	42.7	0.82[b]	5 (351/198)	0.87 (0.66, 1.13)	61.5	0.89[b]
Unfixed	5 (3065/685)	0.65 (0.33, 1.26)	73.1	0.48[b]	4 (2990/683)	0.69 (0.35, 1.36)	78	0.52[b]
Daily dose								
≥10^{10} CFU	11 (3919/1195)	0.92 (0.80, 1.05)	51.1	0.25	6 (2664/877)	1.02 (0.92, 1.14)	6.3	0.11
<10^{10} CFU	12 (3200/1465)	**0.79 (0.68, 0.92)**	75.6		12 (3200/1461)	**0.79 (0.68, 0.92)**	74.5	
Dose frequency								
Single dose	13 (5280/2127)	0.90 (0.81, 1.00)	63.7	0.32	11 (5090/2078)	0.90 (0.80, 1.00)	68.4	0.56
Multiple doses	10 (1839/533)	**0.79 (0.66, 0.95)**	52.4		7 (774/260)	0.77 (0.57, 1.04)	57.3	
Sample size								
≥120	13 (6547/2436)	**0.88 (0.78, 0.98)**	75.8	0.49	11 (5434/2158)	0.89 (0.79, 1.01)	72.4	0.55
<120	10 (572/224)	**0.81 (0.71, 0.93)**	4.6		7 (430/180)	0.81 (0.65, 1.00)	28.5	
Region								
Europe	14 (3325/1554)	**0.85 (0.74, 0.97)**	68.3		13 (3297/1543)	**0.85 (0.74, 0.96)**	69.4	
North America[a]	7 (3509/963)	0.80 (0.64, 1.01)	67.4	0.75	4 (2444/690)	0.78 (0.45, 1.34)	68	0.98
Asia	1 (123/105)	Not pooled	—	—	1 (123/105)	Not pooled	—	—
Oceania	1 (162/38)	Not pooled	—	—	—	Not applicable	—	—
Outcome subtypes								
Respiratory infections	18 (5864/2338)	**0.87 (0.79, 0.97)**	65.7	0.92	—	See overall	—	—
Respiratory symptoms	7 (1952/561)	0.90 (0.80, 1.01)	0		—	Not applicable	—	—
Infection site								
Upper tract	—	Not applicable	—	—	9 (2039/1008)	0.87 (0.76, 1.01)	56.3	
Lower tract	—	Not applicable	—	—	7 (3186/754)	0.81 (0.55, 1.21)	62.5	0.97[c]
Any site	—	Not applicable	—	—	8 (2433/1045)	**0.79 (0.65, 0.95)**	76.3	0.48[c]

Bold numbers indicate statistically significant $P < 0.05$. CI confidence interval; RR relative risk. *P value for heterogeneity of intervention effect between subgroups according to meta-regression analysis. [a] Although the trial by Johnstone *et al.* enrolled participants from the United States, Canada, and Saudi Arabia, it was classified as North American due to the majority of participants being from the United States and Canada. [b] Trials with intervention duration of ≥3 months as a reference group. [c] Upper tract as a reference group.

The certainty of the evidence

The certainty of the evidence was graded as low for all outcomes (ESI Table 5†). All outcomes were downgraded due to suspected publication bias, which was supported by visual inspection and statistical tests for composite respiratory outcomes and respiratory infections; respiratory symptom risk was not assessed due to the limited number of trials but was downgraded nonetheless. Composite respiratory outcomes and respiratory infections were further downgraded for inconsistency due to high heterogeneity, while respiratory symptom risk was additionally downgraded for imprecision.

Secondary outcomes: LGG and respiratory symptom duration

Six RCTs, with 564 in the LGG group and 539 in the control group, were included in the analysis of respiratory symptom duration.[29,39,43,85,91,92] LGG supplementation did not significantly affect respiratory symptom duration (−0.92, 95% CI −2.27, 0.42 days; ESI Fig. 6†), with high heterogeneity (I^2 = 58.5%). Consistently, the corresponding PI (−4.57 to 2.72) was wide and included the null, indicating uncertainty about the consistency of this effect across trials. When the analysis was restricted to five pediatric trials, LGG supplementation reduced respiratory symptom duration (−2.68, 95% CI −4.43, −0.93 days), with low heterogeneity (I^2 = 0%). The certainty of the evidence was deemed as very low due to imprecision, inconsistency, and potential publication bias, which could not be formally assessed due to the limited number of trials (ESI Table 4†).

Discussion

The present meta-analysis, the most comprehensive to date on LGG supplementation and its effects on GI and respiratory outcomes, yields several key findings. LGG supplementation reduced the risk and duration of pediatric diarrhea, with PIs excluding the null, suggesting that future trials are also likely to show benefit. The certainty of evidence for these outcomes was moderate, indicating a reasonable level of confidence in these findings. In contrast, effects on other GI symptoms and respiratory outcomes were more variable, with wider PIs that included the null and generally lower certainty due to inconsistency, imprecision, or suspected publication bias.

Most prior meta-analyses on GI and respiratory outcomes have pooled heterogeneous probiotic strains, often without considering strain-specific effects.[93–97] LGG is one of the most studied strains and possesses distinct features—such as spaCBA-encoded pili that enhance mucosal adherence and immune modulation—not shared by all *Lactobacillaceae* members. Unlike many others, LGG also shows strong acid and bile tolerance and produces specific bioactives that support epithelial barrier function.[4,5] By focusing exclusively on LGG, this meta-analysis provides more targeted estimates of its specific efficacy.

The findings on pediatric diarrhea align with previous meta-analyses supporting the role of LGG supplementation in managing acute diarrhea in children.[6–8] This is particularly relevant in low-income regions where diarrhea remains a major cause of childhood morbidity and mortality.[98] Subgroup analyses suggest benefits in rotavirus-associated diarrhea—a leading cause of severe pediatric diarrhea[99]—especially in areas with low vaccine coverage.[100] Although based on few trials, the shortened duration of rotavirus-related diarrhea with LGG supplementation indicates potential to mitigate this burden. These findings support current clinical guidelines recommending LGG supplementation as an adjunct to oral rehydration therapy.[101]

Beyond diarrhea, LGG supplementation reduced the risk of taste disturbance. While mechanisms are speculative, microbiota-mediated modulation of taste perception has been proposed, potentially involving interactions with GI and oral taste receptors, SCFA production, and the gut–brain axis.[102,103] Given the limited number of trials and potential chance findings, this outcome should be interpreted with caution. No consistent benefits were observed for other GI symptoms (vomiting, nausea, abdominal pain, constipation), underscoring the need to target LGG use to outcomes with demonstrated efficacy.

Compared to an earlier meta-analysis limited to four trials,[13] our meta-analysis includes 18 trials and offers stronger evidence for the preventive effects of LGG supplementation on respiratory infections, especially in children. Reductions in infection risk and symptom duration were observed, although the latter was based on fewer trials. Given the high burden of respiratory infections in children in low- and middle-income countries[104,105]—and their rapid spread in communal settings such as daycare centers[106]—LGG supplementation may offer potential benefits in reducing infection risk during high-transmission periods like winter.[107] LGG supplementation also reduced the risk of upper respiratory tract infections and antibiotic-associated diarrhea in children, the latter often resulting from antibiotic-induced microbiota disruption.[108] However, these findings require confirmation due to limited trial numbers.

While subgroup differences between children and adults were not statistically significant, the effects of LGG supplementation appeared more consistent and robust in children. Significant reductions in diarrhea and respiratory infection risk were primarily observed in pediatric populations, while adult findings were more variable and imprecise—a pattern not clearly addressed in earlier meta-analyses.[6–8,13] This may reflect developmental differences in gut microbiota. Although earlier studies suggested that the microbiota matures by age three, newer evidence indicates maturation continues beyond early childhood,[109] possibly increasing probiotic responsiveness in children.[110–112] In contrast, the adult microbiota tends to be more stable and less amenable to modification. Supporting this, LGG has been shown to colonize the intestines of children more successfully,[113–115] than those of adults.[116] However, the inclusion of broad pediatric age ranges (*e.g.*, 2–16 years) in most trials may obscure age-specific effects, as both diet and microbiota composition vary across developmental stages. Future trials should examine narrower age ranges to better define the optimal window for LGG supplementation.[109,117,118]

Dietary and regional factors may influence the efficacy of LGG supplementation, given their impact on microbiota composition.[119–125] Most included trials lacked dietary data, limiting assessment of diet as an effect modifier. Additionally, the overrepresentation of European trials—where consistent benefits were seen—raises questions about generalizability. Ethnicity, cultural practices, and dietary habits may contribute to regional variation in response. Future trials should collect dietary data and include more diverse populations to clarify these influences.

Although the optimal dose of LGG supplementation is unclear, the present meta-analysis supports the use of $\geq 10^{10}$ CFU daily, as recommended by the European Society for Paediatric, Gastroenterology, Hepatology, and Nutrition,[101] for reducing diarrhea duration and prevents future episodes. Interestingly, lower doses ($<10^{10}$ CFU, mostly 10^9) also reduced diarrhea duration and risk, and prevented respiratory infections in children. Some evidence suggests that LGG can remain viable at lower doses when delivered in certain formulations, such as fermented milk (10^9),[126] enterocoated tablets (10^9),[126] or milk (10^8),[29] indicating that the delivery method may influence the effective dose. However, dosing regimens varied widely across trials (*e.g.*, fixed *vs.* weight-adjusted doses, frequency, and vehicle). Intervention durations also varied, with shorter courses reducing diarrhea and longer ones preventing respiratory infections. This heterogeneity limits comparability and hinders dose–response analysis. Standardizing dose and delivery protocols would enhance comparability and guide clinical application.

LGG supplementation may support GI health by modulating gut microbiota, enhancing epithelial barrier integrity, and regulating mucosal immunity.[127–129] It upregulates tight junction proteins (*e.g.*, occludin, zonula occludens-1),[130–132] potentially reducing intestinal permeability. LGG may also limit colonization by pathogens through competitive adherence,[133–137] antimicrobial peptide production, and enhancement of secretory IgA.[138–140] Together, these actions contribute to gut homeostasis and may help prevent or shorten episodes of diarrhea.

Probiotic intake has been associated with increased production of SCFAs, including acetate, propionate, and butyrate,

which help maintain epithelial integrity and modulate immune responses. These effects are thought to result from shifts in microbial composition toward SCFA-producing taxa and from fermentation of dietary fibers, linking gut microbiota activity to host immune regulation. In the GI tract, SCFAs contribute to homeostasis by enhancing barrier function, reducing local inflammation, and supporting mucosal immunity.[141] Although mechanisms underlying probiotic effects on respiratory health remain under investigation, SCFAs produced in the gut may also exert systemic immunomodulatory effects.[9–12,141] They have been reported to support alveolar macrophage function,[142–144] reduce airway inflammation,[145,146] and influence immune cell differentiation *via* bone marrow signaling and G-protein–coupled receptors.[9–12] Overall, SCFA-mediated mechanisms may contribute to both GI and respiratory outcomes, providing a plausible biological link across systems.

Several limitations should be considered when interpreting these findings. Substantial heterogeneity (I^2 = 67%) was observed for key outcomes, including GI symptom duration, diarrhea risk and duration, and respiratory symptoms. This likely reflects variation in study design, population characteristics (*e.g.*, age groups), and intervention protocols (*e.g.*, LGG dose, duration, and formulation), which may limit the generalizability of pooled estimates. To explore sources of heterogeneity, subgroup and meta-regression analyses were conducted, and PIs were calculated to estimate the range of effects expected in future trials. For most outcomes, the wide PIs—including the null—indicate considerable variability and residual uncertainty. Clinically, this suggests that while benefits are possible, the effectiveness of LGG supplementation may vary across settings and populations, and results from individual trials may differ from pooled estimates. The interpretability of subgroup and meta-regression findings was limited by uneven trial distribution across covariates and a small number of studies in several categories, reducing statistical power and increasing the risk of unstable estimates. Evidence of publication bias was observed for multiple outcomes, including risks and durations of GI and respiratory symptoms, based on funnel plot asymmetry and statistical tests. Although the trim-and-fill method did not identify missing studies, the possibility of overestimated benefits contributed to the downgrading of evidence certainty. In accordance with Cochrane guidelines, heterogeneity and publication bias assessments were only performed when ≥10 trials were available, which restricted their use for some outcomes.

In conclusion, LGG supplementation reduces diarrhea risk and duration in children, supported by moderate-certainty evidence and consistent effects across trials. It may also reduce the risk of respiratory infections in children, although findings were less consistent and based on low-certainty evidence. Heterogeneity, publication bias, and limited trial numbers for other outcomes constrain broader conclusions. While evidence for pediatric diarrhea is more robust, additional well-powered trials are needed to clarify LGG's efficacy across a wider range of outcomes and populations.

Disclosure statement

Y. O., N. L., and W. Z. are employed by SIRIO (Shanghai) Life Technologies Co., Ltd, a contract development and manufacturing organization (CDMO) for the dietary supplement industry. K. H. received financial support from Sirio Pharma Co., Ltd. All other authors report no conflicts of interest. SIRIO (Shanghai) Life Technologies Co., Ltd had final decision rights in the preparation, review, and approval of the manuscript as well as the decision to submit the manuscript for publication. SIRIO (Shanghai) Life Technologies Co, Ltd was not involved in the design and conduct of the study or the collection, management, analysis, and interpretation of the data.

Abbreviations

CI	Confidence interval
GI	Gastrointestinal
GRADE	Grading of recommendations, assessment, development and evaluation
LGG	*Lacticaseibacillus rhamnosus* GG
PICOS	Participants, interventions, comparisons, outcomesand study
PI	Prediction interval
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RoB	Risk of bias
RCT	Randomized controlled trial
RR	Relative risk
SCFA	Short-chain fatty acid
WMD	Weighted mean difference

Author contributions

K. H.: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review & editing, supervision. L. Z.: investigation, data curation, formal analysis, writing – original draft, writing – review & editing. H. W.: investigation, data curation, formal analysis. W. G.: writing – review & editing. L. Q.: conceptualization, methodology, writing – review & editing. Y. O.: supervision, writing – review & editing. N. L.: supervision, writing – review & editing.

Conflicts of interest

Y. O., N. L., and W. Z. are employed by SIRIO (Shanghai) Life Technologies Co., Ltd, a contract development and manufacturing organization (CDMO) for the dietary supplement industry. K. H. received financial support from Sirio Pharma Co., Ltd. All other authors report no conflicts of interest. SIRIO (Shanghai) Life Technologies Co., Ltd had final decision rights in the preparation, review, and approval of the manuscript as

well as the decision to submit the manuscript for publication. SIRIO (Shanghai) Life Technologies Co, Ltd was not involved in the design and conduct of the study or the collection, management, analysis, and interpretation of the data.

Data availability

The data used in this meta-analysis were extracted from previously published studies available in public databases. As these data are derived from existing publications, they are not publicly available as a standalone dataset. However, the compiled dataset used for the analysis can be made available from the corresponding author upon reasonable request.

Acknowledgements

This work was funded by SIRIO (Shanghai) Life Technologies Co., Ltd.

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