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

## Results

### References of the excluded articles

*Relevant outcomes were not investigated*


- Millar MR, Bacon C, Smith SL, Walker V, Hall MA. Enteral feeding of premature infants with Lactobacillus GG. Arch Dis Child. 1993 Nov;69(5 Spec No):483-7.
- Ling WH, Korpela R, Mykkänen H, Salminen S, Hänninen O. Lactobacillus strain GG supplementation decreases colonic hydrolytic and reductive enzyme activities in healthy female adults. J Nutr. 1994 Jan;124(1):18-23.
- Isolauri E, Joensuu J, Suomalainen H, Luomala M, Vesikari T. Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine. 1995 Feb;13(3):310-2.
- Fang H, Elina T, Heikki A, Seppo S. Modulation of humoral immune response through probiotic intake. FEMS Immunol Med Microbiol. 2000 Sep;29(1):47-52.
- Näse L, Hatakka K, Savilahti E, Saxelin M, Pönkä A, Poussa T, Korpela R, Meurman JH. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. Caries Res. 2001 Nov-Dec;35(6):412-20.
- Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. Allergy. 2002 Mar;57(3):243-6.
- Agarwal R, Sharma N, Chaudhry R, Deorari A, Paul VK, Gewolb IH, Panigrahi P. Effects of oral Lactobacillus GG on enteric microflora in low-birth-weight neonates. J Pediatr Gastroenterol Nutr. 2003 Mar;36(3):397-402.
- Colodner R, Edelstein H, Chazan B, Raz R. Vaginal colonization by orally administered Lactobacillus rhamnosus GG. Isr Med Assoc J. 2003 Nov;5(11):767-9.
- Hatakka K, Martio J, Korpela M, Herranen M, Poussa T, Laasanen T, Saxelin M, Vapaatalo H, Moilanen E, Korpela R. Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis--a pilot study. Scand J Rheumatol. 2003;32(4):211-5.
- Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment Pharmacol Ther. 2003 Feb 15;17(4):509-15.
- Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, Savilahti E. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. J Allergy Clin Immunol. 2004 Jul;114(1):131-6.
- Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol. 2004 Mar 15;4:5.
- Bauserman M, Michail S. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. J Pediatr. 2005 Aug;147(2):197-201.

- de Vrese M, Rautenberg P, Laue C, Koopmans M, Herremans T, Schrezenmeir J. Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination. Eur J Nutr. 2005 Oct;44(7):406-13.

- Di Caro S, Tao H, Grillo A, Elia C, Gasbarrini G, Sepulveda AR, Gasbarrini A. Effects of Lactobacillus GG on genes expression pattern in small bowel mucosa. Dig Liver Dis. 2005 May;37(5):320-9.

- Galpin L, Manary MJ, Fleming K, Ou CN, Ashorn P, Shulman RJ. Effect of Lactobacillus GG on intestinal integrity in Malawian children at risk of tropical enteropathy. Am J Clin Nutr. 2005 Nov;82(5):1040-5.

- Kajander K, Hatakka K, Poussa T, Färkkilä M, Korpela R. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. Aliment Pharmacol Ther. 2005 Sep 1;22(5):387-94.

- Petschow BW, Figueroa R, Harris CL, Beck LB, Ziegler E, Goldin B. Effects of feeding an infant formula containing Lactobacillus GG on the colonization of the intestine: a dose-response study in healthy infants. J Clin Gastroenterol. 2005 Oct;39(9):786-90.

- Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. Pediatr Allergy Immunol. 2005 Feb;16(1):65-71.

- Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy. 2005 Apr;60(4):494-500.

- Viljanen M, Pohjavuori E, Haahtela T, Korpela R, Kuitunen M, Sarnesto A, Vaarala O, Savilahti E. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. J Allergy Clin Immunol. 2005 Jun;115(6):1254-9.

- Brouwer ML, Wolt-Plompen SA, Dubois AE, van der Heide S, Jansen DF, Hoijer MA, Kauffman HF, Duiverman EJ. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. Clin Exp Allergy. 2006 Jul;36(7):899-906.

- Hongisto SM, Paajanen L, Saxelin M, Korpela R. A combination of fibre-rich rye bread and yoghurt containing Lactobacillus GG improves bowel function in women with self-reported constipation. Eur J Clin Nutr. 2006 Mar;60(3):319-24.

- Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006 Jun 1;23(11):1567-74.

- Bruzzese E, Raia V, Spagnuolo MI, Volpicelli M, De Marco G, Maiuri L, Guarino A. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. Clin Nutr. 2007 Jun;26(3):322-8.

- Gawrońska A, Dziechciarz P, Horvath A, Szajewska H. A randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. Aliment Pharmacol Ther. 2007 Jan 15;25(2):177-84.

- Manley KJ, Fraenkel MB, Mayall BC, Power DA. Probiotic treatment of vancomycin-resistant enterococci: a randomised controlled trial. Med J Aust. 2007 May 7;186(9):454-7.

- Moreira A, Kekkonen R, Korpela R, Delgado L, Haahtela T. Allergy in marathon runners and effect of Lactobacillus GG supplementation on allergic inflammatory markers. Respir Med. 2007 Jun;101(6):1123-31.

- Szajewska H, Gawronska A, Wos H, Banaszkiewicz A, Grzybowska-Chlebowczyk U. Lack of effect of Lactobacillus GG in breast-fed infants with rectal bleeding: a pilot double-blind randomized controlled trial. J Pediatr Gastroenterol Nutr. 2007 Aug;45(2):247-51.

- Piirainen L, Haahtela S, Helin T, Korpela R, Haahtela T, Vaarala O. Effect of Lactobacillus rhamnosus GG on rBet v1 and rMal d1 specific IgA in the saliva of patients with birch pollen allergy. Ann Allergy Asthma Immunol. 2008 Apr;100(4):338-42.

- Sentongo TA, Cohran V, Korff S, Sullivan C, Iyer K, Zheng X. Intestinal permeability and effects of Lactobacillus rhamnosus therapy in children with short bowel syndrome. J Pediatr Gastroenterol Nutr. 2008 Jan;46(1):41-7.

- Ferrie S, Daley M. Lactobacillus GG as treatment for diarrhea during enteral feeding in critical illness: randomized controlled trial. JPEN J Parenter Enteral Nutr. 2011 Jan;35(1):43-9.

- Baldassarre ME, Laforgia N, Fanelli M, Laneve A, Grosso R, Lifschitz C. Lactobacillus GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone. J Pediatr. 2010 Mar;156(3):397-401.

- Cox MJ, Huang YJ, Fujimura KE, Liu JT, McKean M, Boushey HA, Segal MR, Brodie EL, Cabana MD, Lynch SV. Lactobacillus casei abundance is associated with profound shifts in the infant gut microbiome. PLoS One. 2010 Jan 18;5(1):e8745.

- Francavilla R, Miniello V, Magistà AM, De Canio A, Bucci N, Gagliardi F, Lionetti E, Castellaneta S, Polimeno L, Peccarisi L, Indrio F, Cavallo L. A randomized controlled trial of Lactobacillus GG in children with functional abdominal pain. Pediatrics. 2010 Dec;126(6):e1445-52.

- Szachta P, Ignyś I, Cichy W. An evaluation of the ability of the probiotic strain Lactobacillus rhamnosus GG to eliminate the gastrointestinal carrier state of vancomycin-resistant enterococci in colonized children. J Clin Gastroenterol. 2011 Nov-Dec;45(10):872-7.

- Vajro P, Mandato C, Licenziati MR, Franzese A, Vitale DF, Lenta S, Caropreso M, Vallone G, Meli R. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. J Pediatr Gastroenterol Nutr. 2011 Jun;52(6):740-3.

- Muraro A, Hoekstra MO, Meijer Y, Lifschitz C, Wampler JL, Harris C, Scalabrin DM. Extensively hydrolysed casein formula supplemented with Lactobacillus rhamnosus GG maintains hypoallergenic status: randomised double-blind, placebo-controlled crossover trial. BMJ Open. 2012 Mar 5;2(2):e000637.

- Kumpu M, Lehtoranta L, Roivainen M, Rönkkö E, Ziegler T, Söderlund-Venermo M, Kautiainen H, Järvenpää S, Kekkonen R, Hatakka K, Korpela R, Pitkäranta A. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. J Med Virol. 2013 Sep;85(9):1632-8.

- Pärtty A, Luoto R, Kalliomäki M, Salminen S, Isolauri E. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2013 Nov;163(5):1272-7.e1-2.

- Bruzzese E, Callegari ML, Raia V, Viscovo S, Scotto R, Ferrari S, Morelli L, Buccigrossi V, Lo Vecchio A, Ruberto E, Guarino A. Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial. PLoS One. 2014 Feb 19;9(2):e87796.

- Manzoni P, Meyer M, Stolfi I, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, Decembrino L, Laforgia N, Vagnarelli F, Memo L, Bordignon L, Maule M, Gallo E, Mostert M, Quercia M, Bollani L, Pedicino R, Renzullo L, Betta P, Ferrari F, Alexander T, Magaldi R, Farina D, Mosca F, Stronati M. Bovine lactoferrin supplementation for prevention of

necrotizing enterocolitis in very-low-birth-weight neonates: a randomized clinical trial. Early Hum Dev. 2014 Mar;90 Suppl 1:S60-5.

- Pedersen N, Andersen NN, Végh Z, Jensen L, Ankersen DV, Felding M, Simonsen MH, Burisch J, Munkholm P. Ehealth: low FODMAP diet vs Lactobacillus rhamnosus GG in irritable bowel syndrome. World J Gastroenterol. 2014 Nov 21;20(43):16215-26.

- Tapiovaara L, Lehtoranta L, Swanljung E, Mäkivuokko H, Laakso S, Roivainen M, Korpela R, Pitkäranta A. Lactobacillus rhamnosus GG in the middle ear after randomized, double-blind, placebo-controlled oral administration. Int J Pediatr Otorhinolaryngol. 2014 Oct;78(10):1637-41.

- Kianifar H, Jafari SA, Kiani M, Ahanchian H, Ghasemi SV, Grover Z, Mahmoodi LZ, Bagherian R, Khalesi M. Probiotic for irritable bowel syndrome in pediatric patients: a randomized controlled clinical trial. Electron Physician. 2015 Sep 16;7(5):1255-60.

- Pärtty A, Lehtonen L, Kalliomäki M, Salminen S, Isolauri E. Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. Pediatr Res. 2015 Oct;78(4):470-5.

- Pärtty A, Kalliomäki M, Wacklin P, Salminen S, Isolauri E. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr Res. 2015 Jun;77(6):823-8.

- Korpela K, Salonen A, Virta LJ, Kumpu M, Kekkonen RA, de Vos WM. Lactobacillus rhamnosus GG Intake Modifies Preschool Children's Intestinal Microbiota, Alleviates Penicillin-Associated Changes, and Reduces Antibiotic Use. PLoS One. 2016 Apr 25;11(4):e0154012.

- Berni Canani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C, Granata V, Nocerino R. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. J Allergy Clin Immunol. 2017 Jun;139(6):1906-1913.e4.

- Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, Leong R, Boushey HA, Hilton JF. Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial. Pediatrics. 2017 Sep;140(3):e20163000.

- Gorshein E, Wei C, Ambrosy S, Budney S, Vivas J, Shenkerman A, Manago J, McGrath MK, Tyno A, Lin Y, Patel V, Gharibo M, Schaar D, Jenq RR, Khiabanian H, Strair R. Lactobacillus rhamnosus GG probiotic enteric regimen does not appreciably alter the gut microbiome or provide protection against GVHD after allogeneic hematopoietic stem cell transplantation. Clin Transplant. 2017 May;31(5).

- Bruzzese E, Raia V, Ruberto E, Scotto R, Giannattasio A, Bruzzese D, Cavicchi MC, Francalanci M, Colombo C, Faelli N, Daccò V, Magazzù G, Costa S, Lucidi V, Majo F, Guarino A. Lack of efficacy of Lactobacillus GG in reducing pulmonary exacerbations and hospital admissions in children with cystic fibrosis: A randomised placebo controlled trial. J Cyst Fibros. 2018 May;17(3):375-382.

- Durack J, Kimes NE, Lin DL, Rauch M, McKean M, McCauley K, Panzer AR, Mar JS, Cabana MD, Lynch SV. Delayed gut microbiota development in high-risk for asthma infants is temporarily modifiable by Lactobacillus supplementation. Nat Commun. 2018 Feb 16;9(1):707.

- Esposito C, Roberti A, Turrà F, Cerulo M, Severino G, Settimi A, Escolino M. Frequency of Antibiotic-Associated Diarrhea and Related Complications in Pediatric Patients Who Underwent Hypospadias Repair: a Comparative Study Using Probiotics vs Placebo. Probiotics Antimicrob Proteins. 2018 Jun;10(2):323-328.

- Cabana MD, McKean M, Beck AL, Flaherman V. Pilot Analysis of Early Lactobacillus rhamnosus GG for Infant Colic Prevention. J Pediatr Gastroenterol Nutr. 2019 Jan;68(1):17-19.

- Paparo L, Nocerino R, Bruno C, Di Scala C, Cosenza L, Bedogni G, Di Costanzo M, Mennini M, D'Argenio V, Salvatore F, Berni Canani R. Publisher Correction: Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study. Sci Rep. 2019 Jun 26;9(1):9504.

- Bianchini S, Orabona C, Camilloni B, Berioli MG, Argentiero A, Matino D, Alunno A, Albini E, Vacca C, Pallotta MT, Mancini G, Tascini G, Toni G, Mondanelli G, Silvestri E, Grohmann U, Esposito S. Effects of probiotic administration on immune responses of children and adolescents with type 1 diabetes to a quadrivalent inactivated influenza vaccine. Hum Vaccin Immunother. 2020;16(1):86-94.

- Kumperscak HG, Gricar A, Ülen I, Micetic-Turk D. A Pilot Randomized Control Trial With the Probiotic Strain *Lactobacillus rhamnosus* GG (LGG) in ADHD: Children and Adolescents Report Better Health-Related Quality of Life. Front Psychiatry. 2020 Mar 17;11:181.

- Sanborn VE, Azcarate-Peril MA, Gunstad J. Lactobacillus rhamnosus GG and HbA1c in middle age and older adults without type 2 diabetes mellitus: A preliminary randomized study. Diabetes Metab Syndr. 2020 Sep-Oct;14(5):907-909.

- Savino F, Montanari P, Galliano I, Daprà V, Bergallo M. *Lactobacillus rhamnosus GG* (ATCC 53103) for the Management of Infantile Colic: A Randomized Controlled Trial. Nutrients. 2020 Jun 5;12(6):1693.

- Moludi J, Saiedi S, Ebrahimi B, Alizadeh M, Khajebishak Y, Ghadimi SS. Probiotics Supplementation on Cardiac Remodeling Following Myocardial Infarction: a Single-Center Double-Blind Clinical Study. J Cardiovasc Transl Res. 2021 Apr;14(2):299-307.

- Orłowska E, Czubkowski P, Wołochowska K, Jarzębicka D, Motyl I, Socha P. Assessment of Lactobacillus casei rhamnosus (LGG) therapy in children with biliary atresia - Randomized placebo controlled trial. Clin Res Hepatol Gastroenterol. 2021 Nov;45(6):101753.

- Carucci L, Nocerino R, Paparo L, De Filippis F, Coppola S, Giglio V, Cozzolino T, Valentino V, Sequino G, Bedogni G, Russo R, Ercolini D, Berni Canani R. Therapeutic effects elicited by the probiotic Lacticaseibacillus rhamnosus GG in children with atopic dermatitis. The results of the ProPAD trial. Pediatr Allergy Immunol. 2022 Aug;33(8):e13836.

- Rauseo AM, Hink T, Reske KA, Seiler SM, Bommarito KM, Fraser VJ, Burnham CD, Dubberke ER; CDC Prevention Epicenter Program. A randomized controlled trial of *Lactobacillus rhamnosus* GG on antimicrobial-resistant organism colonization. Infect Control Hosp Epidemiol. 2022 Feb;43(2):167-173.

- Aljumaah MR, Bhatia U, Roach J, Gunstad J, Azcarate Peril MA. The gut microbiome, mild cognitive impairment, and probiotics: A randomized clinical trial in middle-aged and older adults. Clin Nutr. 2022 Nov;41(11):2565-2576.

- Freedman SB, Finkelstein Y, Pang XL, Chui L, Tarr PI, VanBuren JM, Olsen C, Lee BE, Hall-Moore CA, Sapien R, O'Connell K, Levine AC, Poonai N, Roskind C, Schuh S, Rogers A, Bhatt S, Gouin S, Mahajan P, Vance C, Hurley K, Powell EC, Farion KJ, Schnadower D. Pathogen-Specific Effects of Probiotics in Children With Acute Gastroenteritis Seeking Emergency Care: A Randomized Trial. Clin Infect Dis. 2022 Aug 24;75(1):55-64.

- Shulman RJ, Chichlowski M, Orozco FG, Harris CL, Wampler JL, Bokulich NA, Berseth CL. Infant behavioral state and stool microbiome in infants receiving Lactocaseibacillus rhamnosus GG in formula: randomized controlled trial. BMC Pediatr. 2022 Oct 7;22(1):580.

- Luoto R, Pärtty A, Vogt JK, Rautava S, Isolauri E. Reversible aberrancies in gut microbiome of moderate and late preterm infants: results from a randomized, controlled trial. Gut Microbes. 2023 Dec;15(2):2283913.

- Nocerino R, Coppola S, Carucci L, de Giovanni di Santa Severina AF, Oglio F, de Michele R, di Sessa I, Masino A, Bedogni G, Berni Canani R. The step-down approach in children with cow's milk allergy: Results of a randomized controlled trial. Allergy. 2023 Sep;78(9):2477-2486.

- Rasania, M., Shravya, G., Patel, P., Bhil, D., Pathak, S., Bhargava, S. Role of Lactobacillus Rhamnosus GG in Prevention of Necrotizing Entrocolitis and Late Onset Sepsis in Preterm Neonates < 35 Weeks: A Randomized Controlled Trial. Iranian Journal of Neonatology. 2023;14(1):8-17.

- Eliuz Tipici B, Coskunpinar E, Altunkanat D, Cagatay P, Omer B, Palanduz S, Satman I, Aral F. Lactobacillus GG is associated with mucin genes expressions in type 2 diabetes mellitus: a randomized, placebo-controlled trial. Eur J Nutr. 2023 Aug;62(5):2155-2164.

- Hua JL, Yang ZF, Cheng QJ, Han YP, Li ZT, Dai RR, He BF, Wu YX, Zhang J. Prevention of exacerbation in patients with moderate-to-very severe COPD with the intent to modulate respiratory microbiome: a pilot prospective, multi-center, randomized controlled trial. Front Med (Lausanne). 2024 Jan 5;10:1265544.

- Dani C, Biadaioli R, Bertini G, Martelli E, Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. Biol Neonate. 2002 Aug;82(2):103-8.

*Numerical values were not reported*

- Siitonen S, Vapaatalo H, Salminen S, Gordin A, Saxelin M, Wikberg R, Kirkkola AL. Effect of Lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea. Ann Med. 1990 Feb;22(1):57-9.

- Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002 Sep;51(3):405-9.

- Petschow BW, Figueroa R, Harris CL, Beck LB, Ziegler E, Goldin B. Effects of feeding an infant formula containing Lactobacillus GG on the colonization of the intestine: a dose-response study in healthy infants. J Clin Gastroenterol. 2005 Oct;39(9):786-90.

- Kara SS, Volkan B, Erten I. *Lactobacillus rhamnosus* GG can protect malnourished children. Benef Microbes. 2019 Apr 19;10(3):237-244.

*Follow-up of study of original trial*

- Scalabrin D, Harris C, Johnston WH, Berseth CL. Long-term safety assessment in children who received hydrolyzed protein formulas with Lactobacillus rhamnosus GG: a 5-year follow-up. Eur J Pediatr. 2017 Feb;176(2):217-224. (See the original trial Scalabrin 2005)

*Data could not be converted to the preferred format*

- Luoto R, Ruuskanen O, Waris M, Kalliomäki M, Salminen S, Isolauri E. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2014 Feb;133(2):405-13.

*Non-randomized study*

- Marinelli P, Scalese G, Covelli A, Ruffa A, Bedetti G, Bruno G, Severi C. *Lactobacillus rhamnosus* GG supplementation on eradication rate and dyspepsia in *Helicobacter pylori* infection treated with three-in-one bismuth quadruple therapy. Front Microbiol. 2022 Dec 5;13:932331.

*LGG control*

- Kaila M, Isolauri E, Saxelin M, Arvilommi H, Vesikari T. Viable versus inactivated lactobacillus strain GG in acute rotavirus diarrhoea. Arch Dis Child. 1995 Jan;72(1):51-3.

**Gastrointestinal outcomes**

*Characteristics of the included trials*

Sixty-two RCTs were available for GI outcomes. For primary outcomes, 38 RCTs were analyzed for the risk of composite GI outcomes. Twenty-one RCTs involved children, 15 involved adults, and two included both children and adults. Eleven RCTs had intervention durations of three months or longer, 20 had durations of less than three months, and seven had unfixed durations, such as the length of hospitalization. In 25 RCTs, the daily dose of LGG was $\geq 10^{10}$ colony-forming units (CFU), while in 13 RCTs, it was $<10^{10}$ CFU (10 used a daily dose of $10^9$ CFU, and three used $10^8$ CFU). Eighteen RCTs enrolled 120 or more participants, while the others enrolled fewer than 120. Twenty-three RCTs were conducted in Europe, 10 in North America, and the rest in Asia, Oceania, South America, or across multiple regions. Eight RCTs focused on antibiotic-associated outcomes, and four on nosocomial outcomes, while the remaining RCTs did not specify outcome subtypes and could not be categorized. Regarding individual GI outcomes, diarrhea was reported in 24 RCTs, vomiting in 13, nausea in nine, abdominal pain in 12, bloating and constipation in eight trials, loss of appetite and taste disturbances in five trials, and stomach rumbling in three.

For the secondary outcomes, 33 RCTs were analyzed regarding the duration of GI symptoms. The majority of these trials enrolled children, with only three involving adult participants. Nine RCTs reported intervention durations of one week or longer, 13 had durations of less than one week, and 11 applied an unfixed duration (e.g., until the cessation of diarrhea). The daily dose of LGG was $\geq 10^{10}$ CFU in 22 RCTs, $<10^{10}$ CFU in 10 RCTs (with eight administering $10^9$ CFU and two administering $10^8$ CFU) and not reported in one RCT. Seventeen RCTs enrolled 120 or more participants, while the remainder included fewer than 120 participants. Seventeen RCTs were conducted in Europe, seven in Asia, four in North America and South America, and one in Oceania. The outcomes can be categorized into three main subtypes: diarrhea duration, vomiting duration, and the duration of any GI symptoms. Diarrhea duration was the most frequently reported, analyzed in 29 RCTs, followed by vomiting duration in six RCTs, and composite GI symptom duration in four RCTs. Among the RCTs on diarrhea duration, the pre-trial duration of diarrhea was two weeks or longer in three trials, approximately one week in nine trials, five days or shorter in seven trials, and not reported in nine trials; one trial reported participants as being diarrhea-free before the study. Diarrhea etiology was generally not specified, although a few RCTs identified rotavirus, *Clostridioides difficile*, or antibiotics as the cause of diarrhea.

*Risk of bias*

For GI outcomes, 37 of 62 RCTs adequately reported random sequence generation. More than half (54 of 62) appropriately blinded participants and personnel. Nearly half adequately addressed allocation concealment (28 of 62) and outcome assessor blinding (30 of 62). Incomplete outcome data were considered low risk in almost all trials (60 of 62), with attrition rates below 20% after randomization. Reporting bias was deemed low in 13 trials with available protocols and unclear in 49 trials without accessible protocols. The risk of other biases was classified as unclear in all trials, as additional biases could not be definitively ruled out.

**Respiratory outcomes**

*Characteristics of the included trials*

A total of 26 randomized controlled trials (RCTs) were included in the analysis of respiratory outcomes. For primary outcomes, 23 RCTs assessed the risk of composite respiratory outcomes. Fifteen trials focused on children, while the remainder involved adults. Intervention durations varied, with 10 RCTs extending for three months or more, eight lasting less than three months, and five having unfixed durations, such as the length of hospitalization. In 11 trials, the daily dose of LGG was $\geq 10^{10}$ CFU, while 12 trials administered daily doses below $10^{10}$ CFU (seven used $10^9$ CFU, and five used $10^8$ CFU per day

or lower). Thirteen trials enrolled 120 or more participants, while the others included fewer than 120. Fourteen trials were conducted in Europe, six in North America, and the remainder in Asia, Oceania, or across multiple regions. The outcomes were categorized into two main types: respiratory infections and respiratory symptoms. The majority of trials focused on respiratory infections, while only seven assessed respiratory symptoms. Among those investigating infections, outcomes were further classified by infection site. Specifically, nine trials reported data on upper respiratory tract infections, seven on lower respiratory tract infections, and eight on infections at any site.

For the secondary outcomes, six RCTs were included in the analysis of respiratory symptom duration. Five of these trials enrolled children, while one focused on adults. All trials were conducted in Europe, with intervention durations spanning from 3 to 7 months. Half of the trials administered a daily dose of LGG at levels of $\geq 10^{10}$ CFU, while the remaining trials used doses below $10^{10}$ CFU. Only two trials included 120 or more participants, with the others enrolling fewer than 120 participants.

*Risk of bias*

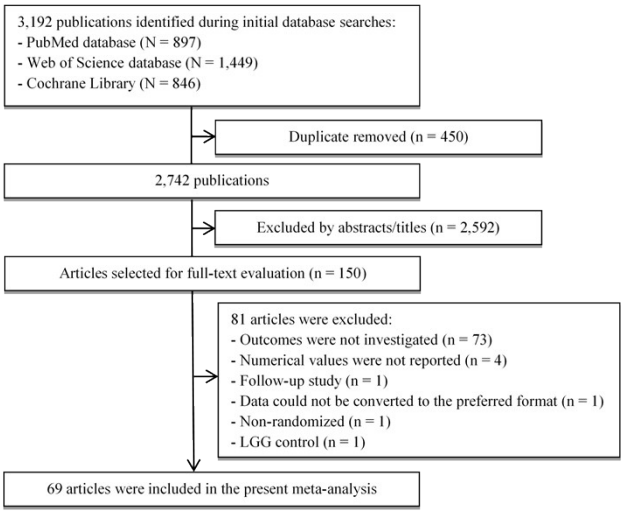
Among the RCTs on respiratory outcomes, more than half have adequately disclosed information on random sequence generation (18 of 26) and allocation concealment (14 of 26) and blinded the outcome assessors (18 of 26), and nearly all have adequately blinded participants and personnel (25 of 26). For incomplete outcome data, % attrition rates of 20% were used as a cut-off point—the attrition rates after the randomization were <20% (low risk) in all RCTs. The risk of reporting bias was low in 14 RCTs with an accessible trial protocol and unclear in 12 RCTs with an inaccessible trial protocol. The risk of other bias was judged as unclear in all RCTs, as it remains unknown if other potential biases exist, and their existence could not be fully ruled out.

**Supplementary tables and figures**

**Supplementary Table 1** Full details of the search strategy‡.

| Database | Step | Search Syntax | Total retrieves |
|---|---|---|---|
| PubMed | 1 | Search (lgg OR lactobacillus rhamnosus GG OR lactobacillus GG OR lactobacillus rhamnosus OR "lacticaseibacillus rhamnosus"[MeSH Terms]) | 7,872 |
| | 2 | Search ("infections" OR symptoms OR respiratory OR "respiratory tract diseases"[MeSH Terms] OR "respiratory tract infections" [MeSH Terms] OR "pneumonia"[MeSH Terms] OR "bronchitis"[MeSH Terms] OR "signs and symptoms, respiratory"[MeSH Terms] OR "cough"[MeSH Terms] OR "rhinorrhea"[MeSH Terms] OR "sneezing"[MeSH Terms] OR "rhinitis"[MeSH Terms] OR "pharyngitis"[MeSH Terms] OR "otitis"[MeSH Terms] OR "sinusitis"[MeSH Terms] OR gastrointestinal OR digestive OR "gastrointestinal diseases"[MeSH Terms] OR "signs and symptoms, digestive"[MeSH Terms] OR "diarrhea"[MeSH Terms] OR "abdominal pain"[MeSH Terms] OR "vomiting"[MeSH Terms] OR "abdominal pain"[MeSH Terms] OR "flatulence"[MeSH Terms] OR "constipation"[MeSH Terms]) | 15,425,802 |
| | 3 | Search (randomly OR randomized) | 1,774,309 |
| | 4 | Search (#1 AND #2 AND #3) | 897 |
| Web of Science | 1 | (lgg OR lactobacillus rhamnosus GG OR lactobacillus GG OR lactobacillus rhamnosus OR lacticaseibacillus rhamnosus) AND (infections OR symptoms OR respiratory OR respiratory tract diseases OR respiratory tract infections OR pneumonia OR bronchitis OR respiratory symptoms OR cough OR rhinorrhea OR sneezing OR rhinitis OR pharyngitis OR otitis OR sinusitis OR gastrointestinal OR digestive OR gastrointestinal infections OR gastrointestinal symptoms OR diarrhea OR abdominal pain OR vomiting OR abdominal pain OR flatulence OR constipation) AND (randomly OR randomized) | 1,449 |
| Cochrane Library | 1 | (lgg OR lactobacillus rhamnosus GG OR lactobacillus GG OR lactobacillus rhamnosus OR lacticaseibacillus rhamnosus) AND (infections OR symptoms OR respiratory OR respiratory tract diseases OR respiratory tract infections OR pneumonia OR bronchitis OR respiratory symptoms OR cough OR rhinorrhea OR sneezing OR rhinitis OR pharyngitis OR otitis OR sinusitis OR gastrointestinal OR digestive OR gastrointestinal infections OR gastrointestinal symptoms OR diarrhea OR abdominal pain OR vomiting OR abdominal pain OR flatulence OR constipation) AND (randomly OR randomized) | 846 |

‡All databases were last searched on May 31, 2024. No restrictions and filters were applied to the searches. In addition to the database searches, the references cited by the retrieved articles were screened for additional RCTs that were missed during the searches. No attempt was made to contact the authors of the retrieved publications for additional information or data, as this approach rarely succeeds.




**Supplementary Figure 1** Flow-chart of the study selection process.

**Supplementary Table 2** Characteristics of the included trials on gastrointestinal outcomes.

| Reference | Country | Age | Participant description | Intervention (N) | Control (N) | Intervention duration | Total daily dose, CFU | Outcome(s) | Results | Key considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| Oksanen et al., 1990 | Finland | ≥ 10 yr (mean: 43.8 yr) | Travelers | LGG powder (373) | Placebo containing ethyl cellulose powder (383) | 1-2 wk | $2x10^9$ | Traveler's diarrhea events (331 cases) | Not significant | Large sample size; potential variability due to the inclusion of both children and adults |
| Raza et al., 1994 | Pakistan | 1-24 months (mean: 1.1 yr) | Children with acute diarrhea | LGG powder mixed in oral rehydration solution (16) | Placebo containing microcrystalline cellulose powder mixed in oral rehydration solution (16) | 2 d | $1x10^{10-11}$ | Diarrhea events on 2nd day (17 cases) | 58% risk reduction for diarrhea | Small sample size |
| Arvola et al., 1999 | Finland | 2 wk to 12.8 yr (mean: 4.8 yr) | Children with respiratory infections receiving antibiotics | LGG powder in capsules + antibiotics (61) | Placebo capsules containing microcrystalline cellulose powder + antibiotics (58) | 7-10 d | $4x10^{10}$ ($2x10^{10}$ b.i.d) | Antibiotic-associated diarrhea events (1.6% C.Difficile and 2.5% Norwalk-like calicivirus; 12 cases) and diarrhea duration | Not significant | Broad age range (spanning across multiple developmental stages) |
| Vanderhoof et al., 1999 | United States | 6 mo to 10 yr (mean: 3.9 yr) | Children with acute infectious disorders receiving antibiotics | LGG powder in capsules ($1x10^{10}$) for those weighing <12 kg or 2 LGG capsules ($2x10^{10}$) for those weighing >12 kg + antibiotics (93) | Placebo capsules containing inulin powder + antibiotics (95) | Until antibiotic courses were completed or diarrhea ceased | $1x10^{10}$ (<12 kg)-$2x10^{10}$ (>12 kg) | Antibiotic-associated diarrhea events (32 cases) and diarrhea duration | 61% risk reduction for diarrhea; 1.2-day shorter duration for diarrhea | Potential variability due to broad age range (spanning across multiple developmental stages) and weight-based dosing |
| Armuzzi et al., 2001 | Italy | Mean: 37 yr | H. Pylori-positive patients undergoing eradication therapy | LGG powder + triple therapy with pantoprazole, clarithromycin, and tinidazole (60) | Triple therapy with pantoprazole, clarithromycin, and tinidazole (60) | 2 wk | $1.2x10^{10}$ ($6x10^9$ b.i.d) | Antibiotic-associated GI symptom events (73 cases) | 70% risk reduction for composite GI outcomes; 70% risk reduction | Not using placebo |

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| | | | | | | | | | for diarrhea; 70% risk reduction for taste disturbance; 60% risk reduction for bloating | |
| Hatakka et al., 2001 | Finland | 1-6 yr (mean: 4.5 yr) | Children attending day care centers | Milk supplemented with LGG (252) | Regular milk (261) | 7 mo | 1-2x$10^8$ (from 200 mL of milk containing 5-10x$10^5$ CFU/mL) | GI symptom events (386 cases) and GI duration | Not significant | Large sample size; long duration |
| Szajewska et al., 2001 | Poland | 1-36 mo (mean: 10.7 mo) | Children hospitalized for reasons other than diarrhea | LGG powder (45) | Placebo powder (36) | For the duration of the hospitalization | 1.2x$10^{10}$ (6x$10^9$ b.i.d) | Nosocomial diarrhea events (23% rotavirus; 15 events) and diarrhea duration | 80% risk reduction for diarrhea | Children confirmed diarrhea-free at baseline, minimizing reverse causation |
| Thomas et al., 2001 | United States | ≥18 yr (mean: 59 yr) | Hospitalized patients receiving antibiotics | LGG powder in capsules + antibiotics (133) | Placebo capsules containing inulin powder + antibiotics (134) | 2 wk | 2x$10^{10}$ (1x$10^{10}$ b.i.d) | Antibiotic-associated diarrhea events (79 cases) | Not significant | Large sample size; broad age range (spanning across different life stages) |
| Cremonini et al., 2002 | Italy | 18-61 yr | H. pylori positive, asymptomatic patients undergoing eradication therapy | LGG powder + triple therapy with pantoprazole, clarithromycin, and tinidazole (60) | Placebo powder + pantoprazole, clarithromycin, and tinidazole (60) | 7 d | 1.2x$10^{10}$ (6x$10^9$ b.i.d) | Antibiotic-associated GI symptom events (12 cases) | 86% risk reduction for loss of appetite; 85% risk reduction for taste disturbance | Broad adult age range (spanning across different life stages); low events |
| Mastretta et al., 2002 | Italy | 1-18 mo (mean: 10 mo) | Children hospitalized for common diseases | LGG powder in capsules (114) | Placebo capsules containing inert oligosaccharides powder (106) | For the duration of the hospitalization | 1x$10^{10}$ | Nosocomial GI infections (51) | Not significant | Large sample size |
| Kirjavainen et al., 2003 | Finland | Mean: 5.5 mo | Infants with atopic diseases | Hydrolyzed whey formula with LGG (14) | Hydrolyzed whey formula (8) | 1.6 mo | 1x$10^9$ per gram of formula; ~3 × $10^{10}$ CFU/kg body weight | GI symptom events (0 cases) | Not significant | Small sample; no events observed; same developmental stage; atopic condition limits |

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| | | | | | | | | | | generalizability; unclear dosing |
| Banaszkiewicz et al., 2005 | Poland | 2-16 yr | Children with constipation | LGG powder in capsules + Lactulose (43) | Placebo powder in capsules + Lactulose (41) | 3 mo | $2x10^9$ ($1x10^9$ b.i.d) | Abdominal pain or vomiting events (9 cases) | Not significant | Wide age range; low events |
| Bousvaros et al., 2005 | United States | Mean: 14.8 | Children with Crohn's disease | LGG powder in capsules (39) | Placebo capsules containing inulin powder (36) | For 2 years or until a clinical relapse was documented | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Vomiting, nausea, or abdominal pain events (5 cases) | Not significant | Broad age range (spanning across multiple developmental stages); atopic condition limits generalizability |
| Folster-Holst et al., 2006 | Germany | 1-55 mo (1.6 yr) | Infants with moderate to severe atopic dermatitis | LGG powder in capsules (26) | Placebo capsules containing microcrystalline cellulose powder (27) | 2 mo | $1x10^{10}$ ($5x10^9$ b.i.d) | Diarrhea, vomiting, or nausea events(15 cases) | Not significant | Broad age range (spanning across multiple developmental stages); atopic condition limits generalizability |
| Grüber et al., 2007 | Germany | 3-12 mo (mean: 7.3 mo) | Infants with mild to moderate atopic dermatitis | LGG, cellulose, saccharose, and magnesium stearate powder in capsules (54) | Placebo capsule containing cellulose, saccharose, and magnesium stearate powder (48) | 3 mo | $1x10^{10}$ ($5x10^9$ b.i.d) | GI symptom events (28 cases) | Not significant | Same developmental stage; atopic condition limits generalizability |
| Kekkonen et al., 2007 | Finland | Mean: 40 yr | Marathon runners | Milk-based fruit drinks containing LGG or LGG powder in capsules (70) | Milk-based fruit drinks or placebo capsules (71) | 3 mo | Capsules: $1x10^{10}$ ($5x10^9$ b.i.d) Drinks: $4x10^{10}$ ($2x10^{10}$ b.i.d) | Diarrhea, vomiting, or abdominal pain events (40 cases) | Not significant | Participants were athletes, limiting generalizability; dosing variation by delivery methods (capsules vs. drinks) may introduce variability |
| Österlund et al., 2007 | Finland | Median: 60 yr | Colorectal cancer patients undergoing chemotherapy | LGG powder in capsules + adjuvant chemotherapy (97) | Adjuvant chemotherapy (51) | 8 mo | $1\text{-}2x10^{10}$ | Chemotherapy-associated diarrhea events (119 cases) | 42% risk reduction for diarrhea | Long duration; high events; cancer limits generalizability; imbalance in the number of |

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| | | | | | | | | | | participants in both group |
| Szajewska et al., 2009 | Poland | 5-17 yr | H. pylori-positive children undergoing eradication therapy | LGG powder + triple therapy with amoxicillin, clarithromycin, and omeprazole (35) | Placebo-containing maltodextrin powder + triple therapy with amoxicillin, clarithromycin, and omeprazole (31) | 1 wk | $2x10^9$ ($1x10^9$ b.i.d) | Antibiotic-associated diarrhea, vomiting, nausea, abdominal pain, constipation, taste disturbance, or loss of appetite events (8 cases) | Not significant | Broad age range (spanning across multiple developmental stages); low events |
| Hojsak et al., 2010 | Croatia | Mean: 10 yr | Hospitalized children free from GI and respiratory infections | Fermented milk supplemented with LGG (376) | Fermented milk (366) | For the duration of the hospitalization | $1x10^9$ | Nosocomial GI infection events (63 cases) | 76% risk reduction for diarrhea | Large sample size; age was not well-defined; children confirmed to be infection-free at baseline, minimizing reverse causation |
| Hojsak et al., 2010 | Croatia | ≥1 yr; Mean: 4.4 yr | Children attending day care centers | Fermented milk supplemented with LGG (139) | Fermented milk (142) | 3 mo | $1x10^9$ | GI infection events (52 cases) and GI symptom duration | Not significant | Large sample size; age was not well-defined |
| Morrow et al., 2010 | United States | Mean: 53.5 yr | Patients requiring mechanical ventilation | LGG powder in capsules (overall: 68; C. difficile: 4) | Placebo capsules containing inulin powder (overall: 70; C. difficile: 13) | Until extubation, tracheostomy placement, or death | $4x10^9$ ($2x10^9$ b.i.d) | C. Difficile and non-C. Difficile diarrhea events (103 cases) and C. Difficile diarrhea duration | Not significant | Critical illness limits generalizability; age was not well-defined |
| Nermes et al., 2010 | Finland | Mean: 6.7 mo | Infants with atopic dermatitis | Hydrolyzed casein formula with LGG (19) | Hydrolyzed casein formula (20) | 3 mo | $3.4x10^9$ (from a formula containing $5.0x10^7$ CFU/g) | GI infection events (2 cases) | Not significant | Small sample size; low events; same developmental stage; atopic condition limits generalizability |
| Davidson et al., 2011 | United States | 18-49 yr (mean: | Adults receiving influenza | LGG powder in capsules (19) | Placebo capsules | 1 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea, abdominal | Not significant | Low sample size; high events; |

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| | | 33.3 yr) | vaccine | | containing inulin powder (20) | | | pain, nausea, bloating, constipation, loss appetite, rumbling, or flatulence events (36 cases) | | broad adult age range (spanning across different life stages) |
| Kumpu et al., 2012 | Finland | 2-6 yr (mean: 4 yr) | Children attending daycare centers | Milk supplemented with LGG (251) | Milk (250) | 7 mo | $1x10^8$ | GI symptom events (423 cases) | Not significant | Large sample size; high events; long duration |
| Kumpu et al., 2013 | Finland | 18-30 yr (mean: 24.1 yr) | Patients requiring tonsillectomy | LGG powder in capsules (13) | Placebo capsules containing hemicellulose powder (15) | 3 wk | $4x10^{10}$ | GI symptom events (3 cases) | Not significant | Small sample sizes |
| Ruiz et al., 2013 | Cuba | Mean: 56.6 yr | H. pylori-positive children undergoing eradication therapy | LGG + triple therapy with amoxicillin, clarithromycin, and omeprazole (29) | Placebo + triple therapy with amoxicillin, clarithromycin, and omeprazole (30) | 2 wk | $1.2x10^{10}$ ($6x10^9$ b.i.d) | Antibiotic-associated GI symptom events (11 cases) | Not significant | Age was not well-defined |
| Bajaj et al., 2014 | United States | 18-65 yr (mean: 57.3 yr) | Patients with cirrhosis | LGG (18) | Placebo (19) | 1 mo | $5.1\text{-}6.1x10^{10}$/g | Diarrhea, abdominal pain, or bloating (10 cases) | Not significant | Atopic condition limits generalizability; unclear dosing reference (the study reports the dose in CFU/gram, but it is unclear whether this refers to a gram of powder, food, liquid, or another vehicle) |
| Sindhu et al., 2014 | India | 0.5-5 yr (median: 1 yr) | Children With Rotavirus and Cryptosporidium gastroenteritis | LGG powder in capsules (64) | Placebo capsules containing microcrystalline cellulose powder (59) | 1 mo | $1x10^{10}$ | Diarrhea events during follow-up and vomiting events (88 cases) and diarrhea duration | Not significant | Broad children age range (spanning across different developmental stages) |

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| Doron et al., 2015 | United States | ≥18 yr (mean: 70 yr) | Adults positive for vancomycin-resistant enterococci | LGG powder in capsules (6) | Placebo capsules containing microcrystalline cellulose powder (5) | 2 wk | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea, abdominal pain, nausea, bloating, or constipation events (9 cases) | Not significant | Broad age range (spanning across different life stages); small sample size |
| Bruzzese et al., 2016 | Italy | 0.5-5 yr (mean: 2.8 yr) | Hospitalized children | Drink containing LGG, vitamin B, vitamin C, and zinc (45) | Placebo drink (45) | 2 wk | $6x10^{9}$ ($3x10^{9}$ b.i.d) | Nosocomial GI infection events (13 cases) | 82% risk reduction for Nosocomial GI infections | Broad age range (spanning across multiple developmental stages) |
| Jensen et al., 2018 | Denmark | 18-65 yr (mean: 46.2 yr) | Chronic low back pain patients with type 1 or mixed Modic changes | LGG capsules (44) | Placebo capsules (45) | 3.3 mo | $1.2x10^{10}$ ($6x10^{9}$ b.i.d) | GI symptom events (8 cases) | Not significant | Broad age range (spanning across different life stages); low events |
| Wang et al., 2018 | Canada | ≥ 65 yr (mean: 85.5 yr) | Nursing home residents | LGG capsules (100) | Placebo capsules containing calcium carbonate (96) | 6 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea, vomiting, or nausea events (59 cases) | Not significant | Long duration; geriatric population |
| Schnadower et al., 2019 | United States | 3 mo-4 yr (median: 1.4 yr) | Children with gastroenteritis | LGG powder in capsules (472) | Placebo capsules (479) | 5 d | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea (45.6% viruses and 15.2% bacteria (incl. 14% rotavirus); <7 d), nausea, bloating, constipation, loss appetite, rumbling, or flatulence events (122 cases) and diarrhea and vomiting duration | Not significant | Large sample size; broad age range (spanning across multiple developmental stages) |
| Basturk et al., 2020 | Turkey | 0-12 mo (mean: 4.4 mo) | Infants with cow's milk protein allergy | LGG drops (48) | Placebo drops (52) | 1 mo | $1x10^{9}$ | Diarrhea, vomiting, abdominal pain, bloating, or constipation events (26 | 83% risk reduction for diarrhea | Same developmental stages; atopic condition limits generalizability |

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| | | | | | | | | cases) | | |
| Dziechciarz et al., 2020 | Poland | 1 mo-5 yr (11.5 mo) | Children gastroesophageal reflux disease | LGG powder + proton pump inhibitors (30) | Placebo powder + proton pump inhibitors (29) | 1-1.5 mo | $2x10^8$ ($1x10^8$ b.i.d) | GI infection events (18 cases) | Not significant | Broad age range (spanning across multiple developmental stages); low-dose LGG |
| Johnstone et al., 2021 | United States, Canada, and Saudi Arabia | ≥18 yr (mean: 59.8 yr) | Critically ill patients requiring mechanical ventilation | LGG capsules (1,318) | Placebo capsules containing microcrystalline cellulose (1,332) | For a maximum 2 months or until discharge from the ICU or until Lactobacillus species were isolated from a sterile site or cultured | $2x10^{10}$ | Diarrhea events (1,716); antibiotic-associated diarrhea events (1,572 cases) | Not significant | Large, multicenter trial; wide age range; critical illness limits generalizability |
| Loke et al., 2022 | Australia | 1-10 yr (5.9 yr) | Children with peanut allergy receiving oral immunotherapy | LGG + oral immunotherapy (79) | Placebo + oral immunotherapy (83) | 18 mo | $2x10^{10}$ | Diarrhea, vomiting, or abdominal pain events (36 cases) | Not significant | Broad age range (spanning across multiple developmental stages); atopic condition limits generalizability |
| Wischmeyer et al., 2024 | United States | ≥ 1 yr | Individuals exposed to someone with confirmed COVID-19 diagnosed within ≤7 d | LGG powder in capsules (91) | Placebo capsules containing microcrystalline cellulose powder (91) | 1 mo | Age <5: $1x10^{10}$; age >5: $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea, abdominal pain, nausea, bloating, constipation, or taste disturbance events (23 cases) | Not significant | Potential variability due to the inclusion of both children and adults; COVID-19 limits generalizability; dosing varied by age |
| Isolauri et al., 1991 | Finland | 4-45 mo | Children with acute diarrhea (82% rotavirus; <1 wk) | Fermented milk supplemented with LGG (24) | Pasteurized yogurt (24) | 5 d | $2x10^{10\text{-}11}$ ($1x10^{10\text{-}11}$ b.i.d) | Diarrhea duration | 1-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); small sample size |
| Kaila et al., 1992 | Finland | 7-37 mo (1.3 yr) | Children with acute rotavirus diarrhea (<1 wk) | Fermented milk supplemented with LGG (22) | Pasteurized yogurt (17) | 5 d | $2x10^{10\text{-}11}$ ($1x10^{10\text{-}11}$ b.i.d) | Diarrhea duration | 1.4-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); small |

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| | | | | | | | | | | sample size; pathogen was specified (rotavirus) |
| Isolauri et al., 1994 | Finland | 5-28 mo (mean: 1.2 yr) | Children with acute rotavirus diarrhea (<1 wk) | LGG powder (21) | No LGG (21) | 5 d | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Diarrhea duration | 0.8-day shorter duration for diarrhea | Small sample size; pathogen was specified (rotavirus) |
| Majaama et al., 1995 | Finland | 4-35 mo (mean: 1.4 yr) | Children with acute rotavirus gastroenteritis (<1 wk) | LGG powder (16) | Lactophilus powder (14) | 5 d | $2x10^{9}$ ($1x10^{9}$ b.i.d) | Diarrhea duration | 1-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); small sample size; pathogen was specified (rotavirus) |
| Pant et al., 1996 | Thailand | 1-24 mo (mean: 8 mo) | Children with acute diarrhea (<2 wk) | LGG powder (14) | Placebo powder containing microcrystalline cellulose (12) | 2 d | $1x10^{10-11}$ | Diarrhea duration | 1.4-day shorter duration for diarrhea | Small sample size |
| Guarino et al., 1997 | Italy | 3-36 mo (mean: 1.6 yr) | Children with mild diarrhea (61% rotavirus; ≤2 d) | Milk or formula supplemented with LGG powder (52) | Oral rehydration solution (48) | 5 d | $6x10^{9}$ ($3x10^{9}$ b.i.d) | Diarrhea duration | 1.6-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); no placebo |
| Shornikova et al., 1997 | Russia | 1-36 mo (mean: 1.06 yr) | Children with acute diarrhea (27% rotavirus and 21% bacteria; <5 d) | LGG powder (59) | Placebo powder containing cellulose (64) | 5 d | $1x10^{10}$ ($5x10^{9}$ b.i.d) | Diarrhea duration | 1.1-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages) |
| Oberhelman et al., 1999 | Peru | 6-24 mo (mean: 1.2 y) | Undernourished children | LGG powder in capsules (99) | Placebo capsules containing microcrystalline cellulose powder (105) | 15 mo | $3.7x10^{10}$ | Diarrhea duration | Not significant | Long duration; undernourishment limits generalizability |
| Guandalini et al., 2000 | Italy | 1-36 mo | Children with acute diarrhea (35% rotavirus and 15% invasive pathogens ) | LGG + oral rehydration solution (147) | Placebo + oral rehydration solution (140) | Until diarrhea ceased | $1x10^{10}$ | Diarrhea duration | 0.57-day shorter duration for diarrhea | Large sample; broad age range (spanning across multiple developmental stages) |
| Jasinski et al., 2002 | Uruguay | 1-36 mo | Children with acute diarrhea | LGG + oral rehydration | Placebo + oral rehydration | 5 d | $1x10^{10}$ | Diarrhea duration | 3-day shorter | age range (spanning across |

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| | | | (40% rotavirus) | solution (45) | solution (52) | | | | duration for diarrhea | multiple developmental stages) |
| Costa-Ribeiro et al., 2003 | Brazil | 1-24 mo (10 mo) | Children with acute, moderately dehydrating diarrhea (50% rotavirus; 3 d) | LGG powder in capsules + oral rehydration solution (61) | Placebo capsules containing inulin powder + oral rehydration solution (63) | Until diarrhea ceased | $1x10^{10}$ | Diarrhea duration | Not significant | Included only males |
| Salazar-Lindo et al., 2004 | Uruguay | 3-36 mo (1.2 yr) | Children with acute diarrhea (32% rotavirus; <2 d) | Milk formula supplemented with LGG (51) | Milk formula (52) | Until diarrhea ceased or a maximum of 5 d | $1 \times 10^{11}$ per serving of milk; 150 mL/kg/day (max 1000 mL/day) | Diarrhea duration | Not significant | Broad age range (spanning across multiple developmental stages); dosing varied by weight |
| Salminen et al., 2004 | Finland | Mean: 44.5 yr | HIV patients on antiretroviral therapy | Juice-milk drink supplemented with LGG (17) | Juice-milk drink (17) | 2 wk | $1\text{-}5x10^{10}$ | Diarrhea duration | Not significant | Low sample size; HIV limits generalizability; age was not well-defined |
| Basu et al., 2007 | India | Mean: 1.9 yr | Children with acute diarrhea (75.8% rotavirus) | LGG powder + oral rehydration solution (323) | Placebo powder + oral rehydration solution (323) | Minimum 7 d or until diarrhea ceased | $1.2x10^{8}$ ($6x10^{7}$ b.i.d) | Diarrhea and vomiting duration | 0.5-day longer duration for combined diarrhea and vomiting | Large sample; low dose; age was not well-defined |
| Basu et al., 2007 | India | Mean: 4.1 yr | Children with persistent diarrhea (E. coli (9%), Shigella spp. (7%), Clostridium difficile (6%), E. histolytica (7%), G. lamblia (5%), and mixed infections (4%); ≥ 14 d) | LGG powder + oral rehydration solution (117) | Placebo powder + oral rehydration solution (118) | Minimum 7 days or until diarrhea ceased | $1.2x10^{8}$ ($6x10^{7}$ b.i.d) | Diarrhea and vomiting duration | 3.9-day shorter duration for diarrhea; 1.9-day shorter duration for combined diarrhea and vomiting | Large sample; low dose; age was not well-defined |
| Canani et al., 2007 | Italy | 3-36 mo | Children with acute diarrhea (<2 d) | LGG solution (100) | Oral rehydration solution (92) | 5 d | $1.2x10^{10}$($6x10^{9}$ b.i.d) | Diarrhea and vomiting duration | 1.2-day shorter duration for diarrhea; 0.6-day shorter duration for | Broad age range (spanning across multiple developmental stages) |

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| | | | | | | | | | combined diarrhea and vomiting | |
| Rautanen et al., 2008 | Finland | 6-36 mo (1.4 yr) | Children with acute diarrhea (<1 wk) | LGG powder + hypotonic oral rehydration solution (28) | Placebo powder + hypotonic oral rehydration solution (31) | For the duration of the hospitalization | $1x10^{10}$ ($5x10^{9}$ b.i.d.) | Diarrhea duration | Not significant | Low sample size; broad age range (spanning across multiple developmental stages) |
| Basu et al., 2007 | India | Mean: 1.6 yr | Children with acute diarrhea (57% rotavirus) | LGG powder + oral rehydration solution (186) | Placebo powder + oral rehydration solution (185) | Minimum 7 day or until diarrhea ceased | $2x10^{12}$ ($1x10^{12}$ b.i.d.) | Diarrhea and vomiting duration | 1-day shorter duration for diarrhea; 1-day shorter duration for combined diarrhea and vomiting | Large sample size; dose-response trial ($10^{12}$ CFU vs $10^{10}$ CFU; the highest dose was selected for meta-analysis) |
| Czerwionka-Szaflarska et al., 2009 | Poland | 2-36 mo | Children with acute diarrhea (55% rotavirus) | LGG + oral rehydration solution (50) | Oral rehydration solution (50) | For the duration of the hospitalization | $5x10^{9}$ in 200 mL solution; administered at 50 mL/kg body weight | Diarrhea duration | 1-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); no placebo |
| Misra et al., 2009 | India | Mean: 1.1 yr | Children with diarrhea (27% rotavirus) | LGG powder in capsules (105) | Placebo capsules containing microcrystalline cellulose powder (105) | 10 d | $1x10^{9}$ | Diarrhea duration | Not significant | Large sample; age was not well-defined |
| Ritchie et al., 2010 | Australia | 4-24 mo (mean: 8.9 mo) | Children with acute diarrhea (<7 d) | LGG capsules (100) | Placebo capsules (100) | 3 d | $1.5x10^{10}$ ($5x10^{9}$ t.i.d.) | Diarrhea duration | Not significant | Large sample size |
| Nixon et al., 2012 | United States | 6-72 mo (2.1 yr) | Children with acute diarrhea (<7 d) | LGG powder in capsules (63) | Placebo capsules containing inulin powder (66) | 5 d | Not reported | Diarrhea and vomiting duration | Not significant | Broad age range (spanning across multiple developmental stages); unclear dosing |
| Aggarwal et al., 2014 | India | 6-60 mo | Children with acute diarrhea (<7 d) | LGG powder in capsules + oral rehydration solution (100) | Oral rehydration solution (100) | 5 d | $1x10^{10}$ | Diarrhea duration | 0.7-day shorter duration for diarrhea | Broad age range (spanning across multiple developmental stages); no |

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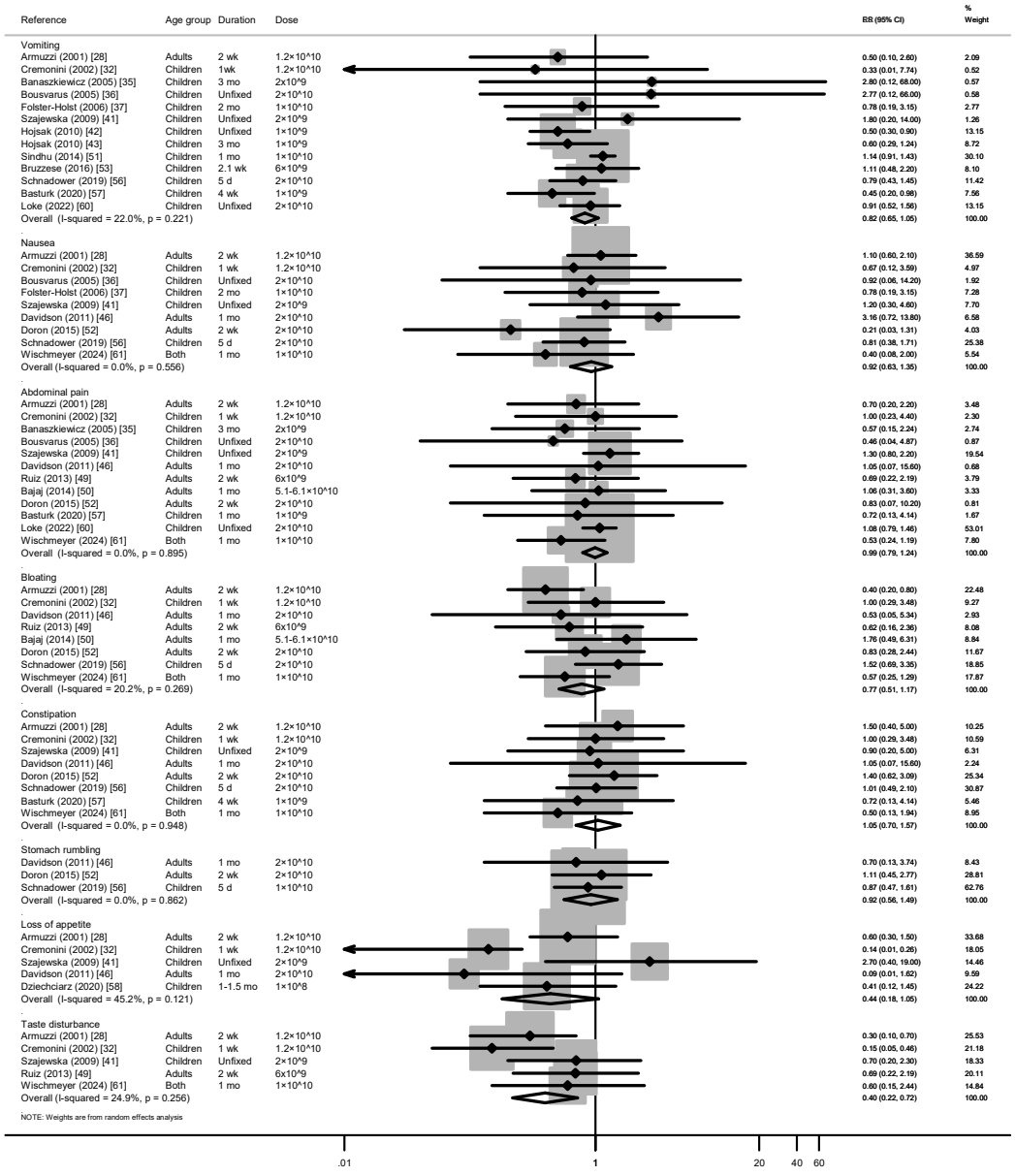
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | placebo |
| Swanjlung et al., 2015 | Finland | 1-5 yr | Children referred to adenotomy | LGG powder in capsules (17) | Placebo capsules containing crystalline cellulose powder (15) | 3 wk | $8\text{-}9x10^9$ | Diarrhea, vomiting, or abdominal pain duration | Not significant | Low sample size; broad age range (spanning across multiple developmental stages) |

**Supplementary Table 3** The methodological quality of the included trials on gastrointestinal outcomes.

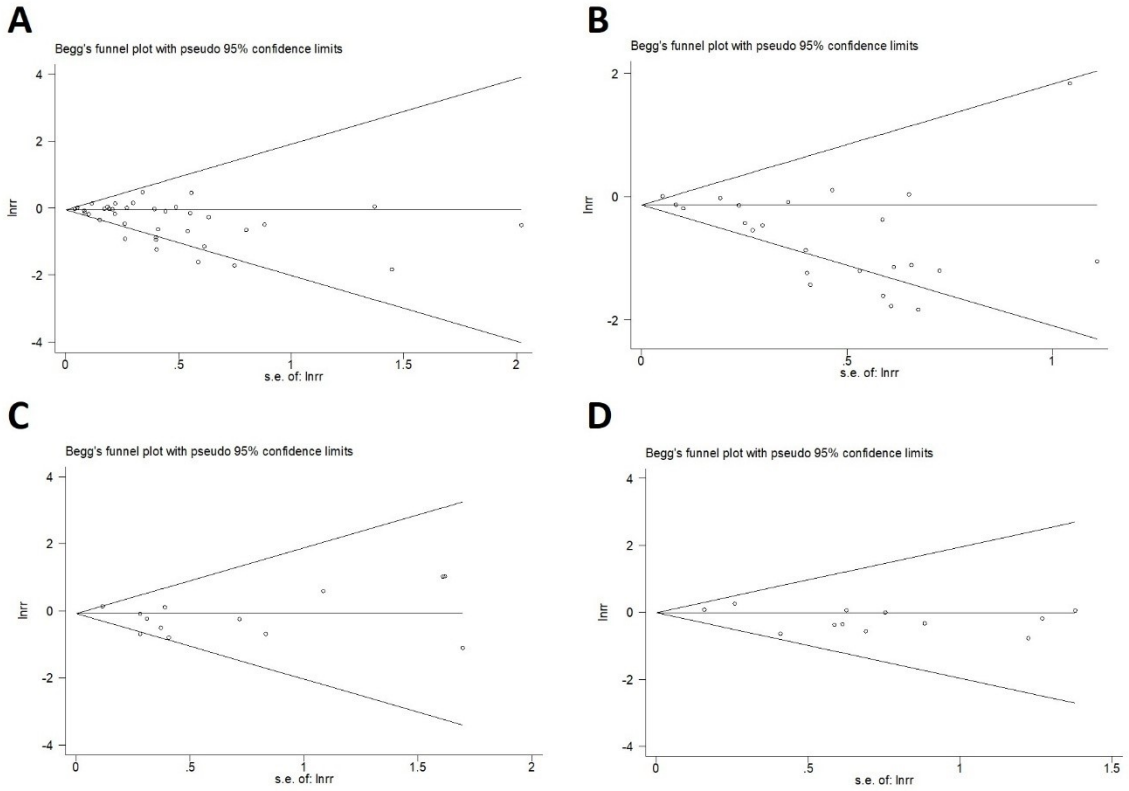
| Study (year) | Selection bias | | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias |
|---|---|---|---|---|---|---|---|
| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | |
| Oksanen et al., 1990 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Raza et al., 1994 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Arvola et al., 1999 | Low risk | Unclear | Low risk | Unclear | High risk | Unclear | Unclear |
| Vanderhoof et al., 1999 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Armuzzi et al., 2001 | Unclear | Low risk | High risk | High risk | Low risk | Unclear | Unclear |
| Hatakka et al., 2001 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Szajewska et al., 2001 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Thomas et al., 2001 | Unclear | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Cremonini et al., 2002 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Mastretta et al., 2002 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Kirjavainen et al., 2003 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Banaszkiewicz et al., 2005 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Bousvaros et al., 2005 | Low risk | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Folster-Holst et al., 2006 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Grüber et al., 2007 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Kekkonen et al., 2007 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Österlund et al., 2007 | Low risk | High risk | High risk | High risk | Low risk | Unclear | Unclear |
| Szajewska et al., | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2009 | | | | | | | |
| Hojsak et al., 2010 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Hojsak et al., 2010 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Morrow et al., 2010 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Nermes et al., 2010 | Unclear | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Davidson et al., 2011 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Kumpu et al., 2012 | Low risk | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Kumpu et al., 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Ruiz et al., 2013 | Unclear | Unclear | Unclear | Unclear | Low risk | Unclear | Unclear |
| Bajaj et al., 2014 | Low risk | Unclear | Unclear | Unclear | Low risk | Unclear | Unclear |
| Sindhu et al., 2014 | Low risk | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Doron et al., 2015 | Low risk | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Bruzzese et al., 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Jensen et al., 2018 | Low risk | Low risk | Low risk | Unclear | Low risk | Low risk | Unclear |
| Wang et al., 2018 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Schnadower et al., 2019 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Basturk et al., 2020 | Unclear | Low risk | Low risk | Unclear | Low risk | Unclear | Unclear |
| Dziechciarz et al., 2020 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Johnstone et al., 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Loke et al., 2022 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Wischmeyer et al., 2024 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Isolauri et al., 1991 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Kaila et al., 1992 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Isolauri et al., 1994 | Unclear | Unclear | High risk | High risk | Low risk | Unclear | Unclear |
| Majaama et al., 1995 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Pant et al., 1996 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Guarino et al., 1997 | Low risk | Unclear | High risk | High risk | Low risk | Unclear | Unclear |
| Shornikova et al., 1997 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Oberhelman et al., 1999 | Low risk | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Guandalini et al., 2000 | Unclear | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Jasinski et al., 2002 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Costa-Ribeiro et al., 2003 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Salazar-Lindo et al., 2004 | Low risk | Low risk | Low risk | Unclear | Low risk | Unclear | Unclear |
| Salminen et al., 2004 | Low risk | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Basu et al., 2007 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Basu et al., 2007 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Canani et al., 2007 | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Unclear |
| Rautanen et al., 2008 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Basu et al., 2007 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Czerwionka-Szaflarska et al., 2009 | Unclear | Unclear | High risk | High risk | Unclear | Unclear | Unclear |
| Misra et al., 2009 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Ritchie et al., 2010 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Nixon et al., 2012 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Aggarwal et al., 2014 | Low risk | Low risk | Low risk | Unclear | Low risk | Low risk | Unclear |
| Swanjlung et al., 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |




**Supplementary Figure 2** The effect of *Lacticaseibacillus rhamnosus* GG supplementation on the risks of vomiting, nausea, abdominal pain, bloating, constipation, stomach rumbling, loss of appetite, and taste disturbance.




**Supplementary Figure 3** Funnel plots of the effect of effects of Lacticaseibacillus rhamnosus GG supplementation on the risks of gastrointestinal symptoms (A), diarrhea (B), vomiting (C), and abdominal pain (D)

**Supplementary Table 4** Sensitivity analyses of the effect 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** |
| Children (<18 yr)[I] | | | | | | | | |
| Overall | 18 (3,717/948) | **0.73 (0.59, 0.91)** | 58.1 | — | 9 (2,502/292) | **0.52 (0.36, 0.76)** | 56.3 | — |
| Intervention duration[a] | | | | | | | | |
| Longer | 7 (1,269/576) | 0.80 (0.54, 1.20) | 68.9 | | 4 (606/135) | **0.57 (0.34, 0.94)** | 22.5 | |
| Shorter | 7 (1,330/228) | 0.72 (0.52, 1.01) | 33.3 | 0.63† | 3 (1,073/107) | **0.74 (0.48, 1.14)** | 28.9 | —⁞ |
| Unfixed | 4 (1,118/144) | **0.60 (0.37,0.99)** | 44.3 | 0.41† | 2 (823/50) | **0.23 (0.12, 0.44)** | 0 | —⁞ |
| Daily dose | | | | | | | | |
| ≥1x10$^{10}$ CFU | 9 (1,799/342) | 0.81 (0.60, 1.09) | 49.3 | 0.33 | 5 (1,289/170) | **0.60 (0.39, 0.93)** | 44.9 | —⁞ |
| <1x10$^{10}$ CFU | 9 (1,918/606) | **0.61 (0.41, 0.92)** | 66.7 | | 4 (1,213/122) | **0.43 (0.21, 0.89)** | 69.7 | |
| Dose frequency | | | | | | | | |
| Single dose | 10 (2,222/723) | **0.68 (0.52, 0.91)** | 65.3 | 0.54 | 5 (1,278/159) | **0.43 (0.27, 0.68)** | 51.2 | —⁞ |
| Multiple doses | 8 (1,495/225) | 0.77 (0.49, 1.19) | 52 | | 4 (1,224/133) | 0.71 (0.39, 1.26) | 49.9 | |
| Sample size | | | | | | | | |
| ≥120 | 7 (2,980/800) | 0.80 (0.63, 1.01) | 64.8 | 0.38 | 4 (2,097/187) | **0.59 (0.38, 0.92)** | 59.4 | —⁞ |
| <120 | 11 (737/148) | **0.61 (0.39, 0.95)** | 46.2 | | 5 (405/105) | **0.45 (0.22, 0.89)** | 59.9 | |
| Region | | | | | | | | |
| Europe | 13 (2,374/725) | **0.69 (0.51, 0.93)** | 64.3 | | 6 (1,396/165) | **0.43 (0.24, 0.79)** | 63.2 | |
| Asia | 2 (155/60) | **0.57 (0.38, 0.87)** | 0 | 0.47‡ | 2 (155/60) | **0.57 (0.38, 0.87)** | 0 | —⁞ |
| North America | 2 (1,026/127) | 0.96 (0.69, 1.34) | 0 | 0.55‡ | 1 (951/67) | Not pooled | — | —⁞ |
| Oceania | 1 (162/36) | Not pooled | — | — | — | Not applicable | — | —⁞ |
| Outcome subtypes | | | | | | | | |
| Nosocomial | 4 (1,133/152) | **0.49 (0.26, 0.91)** | 64.1 | 0.20 | 3 (913/73) | **0.37 (0.14, 1.03)** | 75.8 | —⁞ |
| Unspecified or other | 14 (2,584/796) | **0.80 (0.64, 0.99)** | 50.4 | | 6 (1,589/219) | **0.61 (0.43, 0.87)** | 38.5 | |
| Adults (≥18 yr)[II] | | | | | | | | |
| Overall | 11 (3,990/2,489) | 0.98 (0.92, 1.04) | 0 | — | 6 (3,023/1,956) | 0.89 (0.70, 1.12) | 53.5 | —⁞ |
| Intervention duration[a] | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Longer | 6 (1,124/622) | 0.99 (0.91, 1.07) | 0 | | 3 (224/130) | 0.95 (0.22, 4.04) | 61.8 | |
| Shorter | 3 (78/48) | 0.88 (0.48, 1.59) | 13.1 | 0.95† | 1 (11/7) | Not pooled | — | —⁞ |
| Unfixed | 2 (2,788/1,819) | 0.93 (0.77, 1.13) | 66.9 | 0.68† | 2 (2,788/1,819) | 0.93 (0.77, 1.13) | 66.9 | —⁞ |
| Daily dose | | | | | | | | |
| ≥1x10$^{10}$ CFU | 9 (3,339/2,000) | 0.99 (0.92, 1.08) | 0 | 0.58 | 5 (2,885/1,853) | 0.91 (0.58, 1.42) | 51 | —⁞ |
| <1x10$^{10}$ CFU | 2 (651/489) | 0.93 (0.78, 1.11) | 62.3 | | 1 (138/103) | Not pooled | — | |
| Dose frequency | | | | | | | | |
| Single dose | 5 (3,376/2,234) | 0.99 (0.93, 1.06) | 0 | 0.35 | 3 (2,835/1,842) | 0.94 (0.51, 1.75) | 72.3 | —⁞ |
| Multiple doses | 6 (614/255) | 0.91 (0.79, 1.06) | 0 | | 3 (188/114) | 0.84 (0.69, 1.01) | 0 | |
| Sample size | | | | | | | | |
| ≥120 | 5 (3,786/2,423) | 0.98 (0.92, 1.04) | 0 | 0.80 | 3 (2,936/1,938) | 0.87 (0.69, 1.09) | 69.5 | —⁞ |
| <120 | 5 (204/66) | 1.02 (0.75, 1.40) | 0 | | 3 (87/18) | 1.32 (0.36, 4.83) | 47.2 | |
| Region | | | | | | | | |
| Europe | 5 (919/556) | 0.98 (0.90. 1.06) | 0 | 0.99 | 2 (159/126) | 0.72 (0.40, 1.31) | 31.7 | —⁞ |
| North America[b] | 6 (3,071/1,933) | 0.98 (0.90, 1.07) | 0 | | 4 (2,864/1,830) | 0.94 (0.74, 1.20) | 57.7 | |

Bold numbers indicate statistically significant P <0.05

[I]All analyses performed by excluding trials on antibiotic-associated events and trials in adults (≥18 yr)

[II]All analyses performed by excluding trials on antibiotic-associated events and trials in children (< 18 yr)

*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.

†Trials with longer duration as a reference group

‡Trials conducted in Europe as a reference group

§Trials on unspecified or other outcome as a reference group

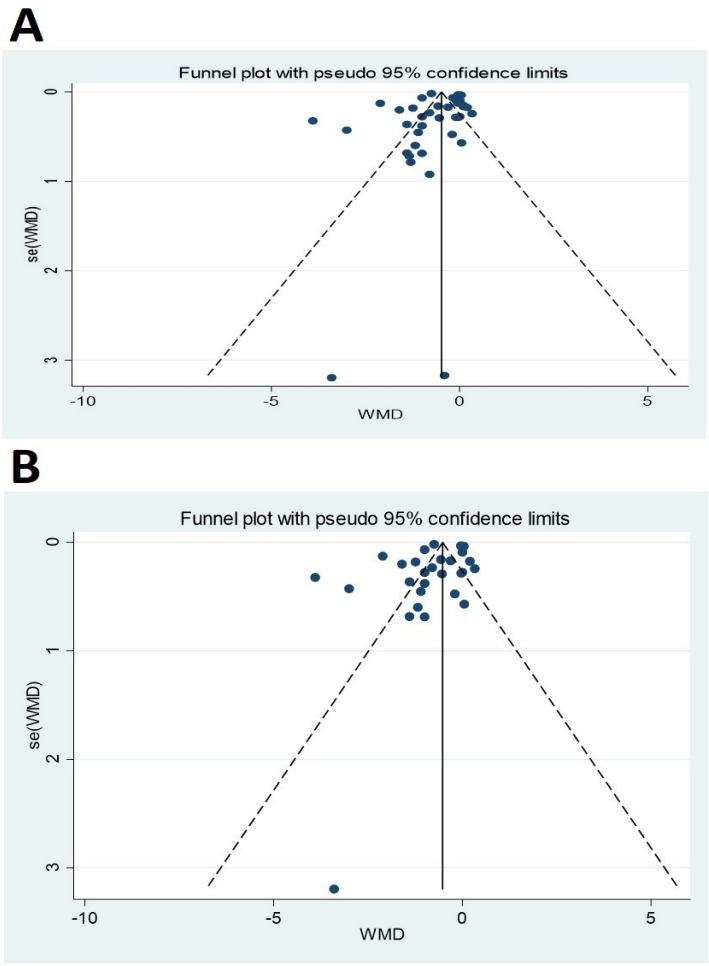
┼Trials on diarrhea as a reference group

⁞Meta-regression analyses were not performed due to limited number of trials (i.e., n ≤10)

CI confidence interval; RR relative risk

**Supplementary Table 5** The certainty of the evidence for the effect of LGG supplementation on each outcome.

| | Effect size (95% CI) | No. studies (total participants /events) for risk; No. studies (sample size) | Risk of bias | Imprecision | Inconsistency | Directness | Publication bias | Quality of evidence |
|---|---|---|---|---|---|---|---|---|
| Composite GI outcome risk | RR: 0.88 (0.81, 0.96) | 38 (9,507/4,084) | Not serious | Not serious | Serious | Not serious | Serious | Low |
| Diarrhea risk | RR: 0.64 (0.52, 0.77) | 24 (7,325/2,717) | Not serious | Not serious | Not serious | Not serious | Serious | Moderate |
| Vomiting risk | RR: 0.82 (0.65, 1.05) | 13 (2,939/307) | Not serious | Serious | Not serious | Not serious | Not serious | Moderate |
| Nausea risk | RR: 0.92 (0.63, 1.35) | 9 (1,589/91) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Abdominal pain risk | RR: 0.99 (0.79, 1.24) | 12 (978/178) | Not serious | Serious | Not serious | Not serious | Not serious | Moderate |
| Bloating risk | RR: 0.77 (0.51, 1.17) | 8 (1,441/120) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Constipation risk | RR: 1.05 (0.70, 1.57) | 8 (1,512/74) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Stomach rumbling risk | RR: 0.92 (0.56, 1.49) | 3 (1,001/51) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Loss of appetite risk | RR: 0.44 (0.18, 1.05) | 5 (327/40) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Taste disturbance risk | RR: 0.40 (0.22, 0.72) | 5 (470/57) | Serious | Serious | Not serious | Not serious | Serious | Low |
| GI symptom duration | -0.62 (-0.81, -0.44) days | 33 (5,880) | Not serious | Not serious | Serious | Not serious | Serious | Low |
| Diarrhea duration | -0.83 (-1.06, -0.59) days | 29 (4,935) | Not serious | Not serious | Not serious | Not serious | Serious | Moderate |
| Vomiting duration | -0.08 (-0.16, 0.01) | 6 (2,587) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Composite respiratory outcome risk | RR: 0.86 (0.78, 0.94) | 23 (7,119/2,660) | Not serious | Not serious | Serious | Not serious | Serious | Low |
| Respiratory infection risk | RR: 0.87 (0.79, 0.97) | 18 (5,864/2,338) | Not serious | Not serious | Serious | Not serious | Serious | Low |
| Respiratory symptom risk | RR: 0.90 (0.80, 1.01) | 7 (1,952/561) | Not serious | Serious | Not serious | Not serious | Serious | Low |
| Respiratory symptom duration | RR: -0.92 (-2.27, 0.42) days | 6 (1,103) | Not serious | Serious | Serious | Not serious | Serious | Low |




**Supplementary Figure 4** Funnel plots of the effects of Lacticaseibacillus rhamnosus GG supplementation on the duration of gastrointestinal symptoms (A) and diarrhea (B)

**Supplementary Table 6** Sensitivity analyses of the effect of *Lacticaseibacillus rhamnosus* GG supplementation on the duration of gastrointestinal symptoms and diarrhea[I].

| | Gastrointestinal symptoms | | | | Diarrhea | | | |
|---|---|---|---|---|---|---|---|---|
| | Trials (participants) | WMD (95% CI), days | $I^2$ (%) | *P** | Trials (participants) | WMD (95% CI), days | $I^2$ (%) | *P** |
| Overall | 28 (5,403) | **-0.62 (-0.81, -0.43)** | 93.9 | — | 25 (4,577) | **-0.84 (-1.09, -0.60)** | 97.9 | — |
| Intervention duration | | | | | | | | |
| ≥1 week | 6 (1,364) | -0.13 (-0.33, 0.07) | 21.6 | | 3 (538) | -0.09 (-0.29, 0.11) | 24.1 | |
| <1 week | 13 (2,033) | **-0.97 (-1.32, -0.63)** | 95.1 | 0.06† | 13 (2,033) | **-1.06 (-1.43, -0.69)** | 97.5 | 0.04† |
| Unfixed | 9 (2,006) | **-0.47 (-0.90, -0.04)** | 96.9 | 0.59† | 9 (2,006) | **-0.86 (-1.46, -0.26)** | 98.5 | 0.34† |
| Daily dose | | | | | | | | |
| ≥1x$10^{10}$ CFU | 18 (3,127) | **-0.53 (-0.72, -0.34)** | 92.9 | | 18 (3,127) | **-0.72 (-1.00, -0.44)** | 98.2 | |
| <1x$10^{10}$ CFU | 9 (2,147) | **-0.80 (-1.38, -0.22)** | 95 | 0.59 | 6 (1,321) | **-1.24 (-2.00, -0.48)** | 96.7 | 0.31 |
| Not reported | 1 (129) | Not pooled | — | — | 1 (129) | Not pooled | — | — |
| Dose frequency | | | | | | | | |
| Single dose | 12 (2,198) | **-0.59 (-0.90, -0.29)** | 95.9 | | 9 (1,372) | **-0.64 (-0.98, -0.30)** | 98.4 | |
| Multiple doses | 15 (3,076) | **-0.67 (-1.03, -0.32)** | 92.9 | 0.96 | 15 (3,076) | **-0.96 (-1.53, -0.38)** | 97.4 | 0.61 |
| Not reported | 1 (129) | Not pooled | — | — | 1 (129) | Not pooled | — | — |
| Sample size | | | | | | | | |
| ≥120 | 13 (4,582) | **-0.95 (-1.32, -0.58)** | 83.3 | 0.07 | 12 (3,788) | **-0.95 (-1.33, -0.58)** | 84.7 | 0.69 |
| <120 | 15 (821) | **-0.35 (-0.81, -0.43)** | 93.3 | | 13 (789) | **-0.76 (-1.10, -0.42)** | 98.8 | |
| Region | | | | | | | | |
| Europe | 14 (1,927) | **-0.85 (-1.07, -0.63)** | 63.8 | | 11 (1,101) | **-0.98 (-1.19, -0.77)** | 60.8 | |
| Asia | 7 (1,812) | **-0.53 (-0.96, -0.10)** | 94.7 | 0.24‡ | 7 (1,812) | **-1.12 (-1.73, -0.50)** | 98.1 | 0.71‡ |
| North America | 2 (1,072) | -0.01 (-0.06, 0.05) | 0 | **0.03‡** | 2 (1,072) | 0.04 (-0.03, 0.11) | 0 | **0.01‡** |
| South America | 4 (528) | -0.59 (-1.45, 0.27) | 94 | 0.49‡ | 4 (528) | -0.59 (-1.45, 0.27) | 94 | 0.40‡ |
| Oceania | 1 (64) | Not pooled | — | — | 1 (64) | Not pooled | — | — |
| Outcome subtypes | | | | | | | | |
| Diarrhea | 25 (4,577) | **-0.84 (-1.09, -0.60)** | 97.9 | | — | See overall | — | — |
| Vomiting | 6 (2,587) | -0.08 (-0.16, 0.01) | 12.3 | 0.04┼ | — | Not applicable | — | — |
| Any | 2 (313) | -1.14 (-2.24, -0.03) | 0 | 0.80┼ | — | Not applicable | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pre-trial diarrhea duration | | | | | | | | |
| ≥14 days | — | Not applicable | — | — | 2 (261) | **-2.72 (-5.17, -0.28)** | 90.8 | |
| ≤7 days | — | Not applicable | — | — | 9 (1,554) | **-0.67 (-1.10, -0.25)** | 98.1 | **<0.01**§ |
| ≤5 days | — | Not applicable | — | — | 7 (1,026) | **-0.98 (-1.62, -0.34)** | 96.3 | 0.11§ |
| Not reported | — | Not applicable | — | — | 6 (1,655) | -0.55 (-1.23, 0.12) | 97.9 | 0.05§ |
| Free from diarrhea | — | Not applicable | — | — | 1 (81) | Not pooled | — | — |
| Etiology | | | | | | | | |
| Rotavirus | — | Not applicable | — | — | 7 (374) | **-0.98 (-1.47, -0.48)** | 94.5 | 0.73± |
| Any or unknown pathogens or unspecified etiology | — | Not applicable | — | — | 22 (4,466) | **-0.82 (-1.08, -0.55)** | 98.1 | |
| Rotavirus positive proportion | | | | | | | | |
| 100% | — | Not applicable | — | — | 7 (374) | **-0.98 (-1.47, -0.48)** | 94.5 | |
| ≥50% to <100% | — | Not applicable | — | — | 10 (1,976) | **-0.69 (-1.04, -0.34)** | 98.6 | 0.42‖ |
| <50% | — | Not applicable | — | — | 8 (1,870) | **-0.65 (-1.12, -0.17)** | 91.1 | 0.51‖ |
| None or not reported | — | Not applicable | — | — | 4 (620) | -1.63 (-3.58, 0.32) | 95.2 | 0.39‖ |

Bold numbers indicate statistically significant P <0.05

[l]The analyses were performed by omitting the trials in adults (≥18 yr) and the trials on antibiotic-associated events

*P value for heterogeneity of intervention effect between subgroups according to meta-regression analysis

†Trials with intervention duration of ≥1 week as a reference group

‡Trials conducted in Europe as a reference group

┼Trials on diarrhea as a reference group

§Pre-trials diarrhea duration of ≥14 days as a reference group

±Rotavirus as a reference group

‖100% as a reference group

CI confidence interval; WMD weighted mean difference

**Supplementary Table 7** Characteristics of the included trials on respiratory outcomes.

| Reference | Country | Age | Participant description | Intervention (N) | Control (N) | Intervention duration | Daily CFU dose of LGG | Outcome | Results | Key considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| Hatakka et al., 2001 | Finland | 1-6 yr (mean: 4.5 yr) | Children attending day care centers | Milk supplemented with LGG (252) | Regular milk (261) | 7 mo | 1-2x$10^8$ (from 200 mL of milk containing 5-10x$10^5$ CFU/mL) | URTI and LRTI events (220 cases) and respiratory symptom (fever, runny nose, sore throat, cough, wheezing, or earache) duration | Not significant | Large sample size; high events; long duration |
| Bousvaros et al., 2005 | United States | Mean: 14.8 | Children with Crohn's disease | LGG powder in capsules (39) | Placebo capsules containing inulin powder (36) | For 2 years or until a clinical relapse was documented | 2x$10^{10}$ (1x$10^{10}$ b.i.d) | Sore throat and headache events (2 cases) | Not significant | Broad age range (spanning across multiple developmental stages); low events; atopic condition limits generalizability |
| Grüber et al., 2007 | Germany | 3-12 mo (mean: 7.3 mo) | Infants with mild to moderate atopic dermatitis | LGG, cellulose, saccharose, and magnesium stearate powder in capsules (54) | Placebo capsules containing cellulose, saccharose, and magnesium stearate powder (48) | 3 mo | 1x$10^{10}$ (5x$10^9$ b.i.d) | URTI and LRTI events (65 cases) | Not significant | Same developmental stage; high events; atopic condition limits generalizability |
| Honeycutt et al., 2007 | United States | 0->24 mo | Children admitted to the intensive care unit | LGG powder in capsules (31) | Placebo capsules containing inulin powder (30) | For the duration of the hospitalization | 1x$10^{10}$ | Nosocomial pneunomia and tracheobronchitis events (7 cases) | Not significant | Low events; critical illness limits generalizability |
| Kekkonen et al., 2007 | Finland | Mean: 40 yr | Marathon runners | Milk-based fruit drink containing LGG (70) | Milk-based fruit drink (71) | 3 mo | Capsules: 1x$10^{10}$ (5x$10^9$ b.i.d) Drinks: 4x$10^{10}$ (2x$10^{10}$ b.i.d) | URTI events (58 cases) | Not significant | Participants were athletes, limiting generalizability; dosing variation by delivery methods (capsules vs. drinks) |
| Scalabrin et al., 2009 | United States | 38-42 wk | Healthy term infant | Hydrolyzed casein formula | Hydrolyzed casein formula | 4.5 mo (from age 14 d to | 1x$10^8$/g of formula | URTI events (33 cases) | Not significant | Same developmental |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | supplemented with LGG (63) | (70) | 150 d) | | | | stages; unclear dosing (formula intake amount not reported) |
| Hojsak et al., 2010 | Croatia | Mean: 10 yr | Hospitalized children free from GI and respiratory infections | Fermented milk supplemented with LGG (376) | Fermented milk (366) | For the duration of the hospitalization | $1x10^9$ | Nosocomial URTI and LRTI events (28 cases) | 62% risk reduction for respiratory infections | Large sample size; age was not well-defined; children confirmed to be infection-free at baseline, minimizing reverse causation |
| Hojsak et al., 2010 | Croatia | Mean: 4.4 yr | Children attending day care centers | Fermented milk supplemented with LGG (139) | Fermented milk (142) | 3 mo | $1x10^9$ | URTI and LRTI events (156 cases) and respiratory symptom (fever, rhinitis, sore throat, cough, wheezing, or earache) duration | 27% risk reduction for respiratory infections | Large sample size; large events; age was not well-defined |
| Morrow et al., 2010 | United States | Mean: 53.5 yr | Patients requiring mechanical ventilation | LGG powder in capsules (overall: 68; C. difficile: 4) | Placebo capsules containing inulin powder (overall: 70; C. difficile: 13) | Until extubation, tracheostomy placement, or death | $4x10^9$ ($2x10^9$ b.i.d) | Ventilator-associated pneumonia events (41 cases) | 52% risk reduction for pneumonia | Critical illness limits generalizability; age was not well-defined |
| Nermes et al., 2010 | Finland | Mean: 6.7 mo | Infants with atopic dermatitis | Hydrolyzed casein formula with LGG (19) | Hydrolyzed casein formula (20) | 3 mo | $3.4x10^9$ (from a formula containing $5.0x10^7$ CFU/g) | URTI and LRTI events (15 cases) | Not significant | Small sample size; low events; same developmental stage; atopic condition limits generalizability |
| Davidson et al., 2011 | United States | 18-49 yr (mean: 33.3 yr) | Adults receiving influenza vaccine | LGG powder in capsules (19) | Placebo capsules containing inulin powder (20) | 1 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Runny nose, cough, sore throat, fever, chills, headache, or myalgia (35 cases) | 20% risk reduction for respiratory symptoms (combined runny nose, cough, sore throat, fever, chills, headache, and myalgia) | Low sample size; high events; broad age range (spanning across different life stages) |
| Kumpu et | Finland | 2-6 yr | Children attending day | Milk | Milk (250) | 7 mo | $1x10^8$ | Respiratory | Not significant | Large sample |

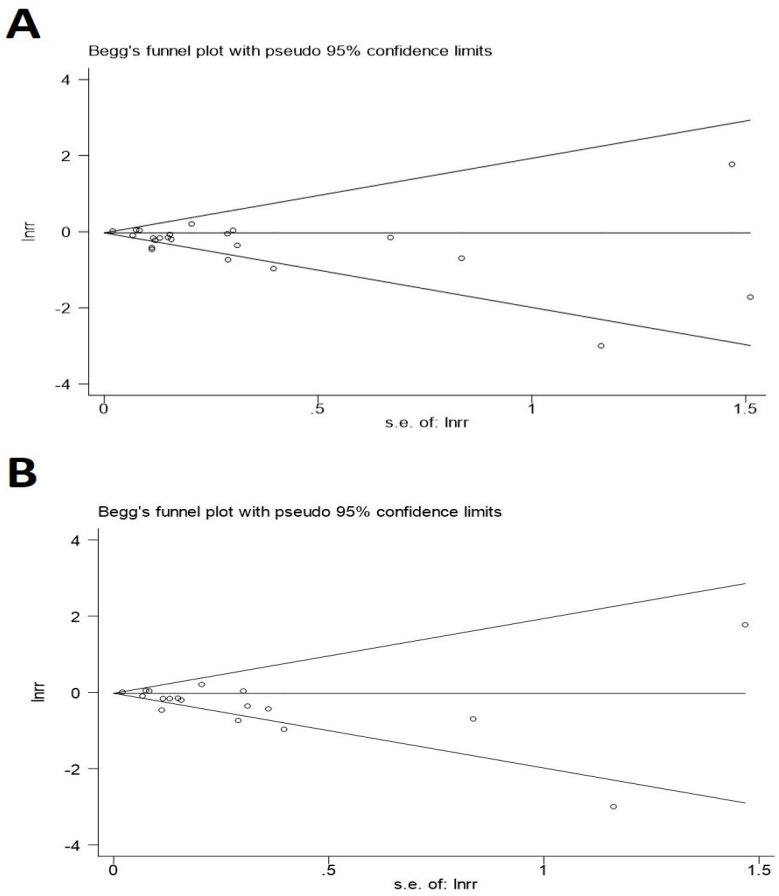
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| al., 2012 | | (mean: 4 yr) | care centers | supplemented with LGG (251) | | | | symptom and infection events (479 cases) | | size; large events; long duration |
| Kumpu et al., 2013 | Finland | 18-30 yr (mean: 24.1 yr) | Patients requiring tonsillectomy | LGG powder in capsules (13) | Placebo capsules containing hemicellulose powder (15) | 3 wk | $4x10^{10}$ | Respiratory symptom events (3 cases) | Not significant | Small sample size |
| Sindhu et al., 2014 | India | 0.5-5 yr (median: 1 yr) | Children With Rotavirus and Cryptosporidium gastroenteritis | LGG powder in capsules (64) | Placebo capsules containing microcrystalline cellulose powder (59) | 1 mo | $1x10^{10}$ | URTI events (104 cases) | Not significant | Broad children age range (spanning across different developmental stages) |
| Kumpu et al., 2015 | Finland | 18-65 yr | Subjects an intranasal inoculation with experimental rhinovirus | Fruit juice supplemented with LGG (19) | Fruit juice (20) | 1.4 mo | $1x10^{9}$ | Cold events (32 cases) | Not significant | Low sample size; high events; broad age range (spanning across different life stages) |
| Bruzzese et al., 2016 | Italy | 0.5-5 yr (mean: 2.8 yr) | Hospitalized children | Drink containing LGG, vitamin B, vitamin C, and zinc (45) | Placebo drink (45) | 2 wk | $6x10^{9}$ | Nosocomial URTI events (6 cases) | Not significant | Broad age range (spanning across multiple developmental stages) |
| Wang et al., 2018 | Canada | ≥ 65 yr (mean: 85.5 yr) | Nursing home residents | LGG capsules (100) | Placebo capsules containing calcium carbonate (96) | 6 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Respiratory symptom and infection events (125 cases) | 34% risk reduction for combined respiratory symptoms and infections; 35% risk reduction for respiratory infections | Long duration; geriatric population |
| Schnadower et al., 2019 | United States | 3 mo-4yr (median: 1.4 yr) | Children with gastroenteritis | LGG powder in capsules (472) | Placebo capsules (479) | 5 d | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Runny nose, cough, sore throat, fever, headache, or myalgia events (146 cases) | Not significant | Large sample size; broad age range (spanning across multiple developmental stages) |
| Dziechciarz et al., 2020 | Poland | <5 yr (mean: 11.5 mo) | Children gastroesophageal reflux disease | LGG powder + proton pump inhibitors (30) | Placebo powder + proton pump inhibitors (29) | 1-1.5 mo | $2x10^{8}$ ($1x10^{8}$ b.i.d) | URTI and LRTI events (47 cases) | Not significant | Broad age range (spanning across multiple developmental stages); low-dose |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | LGG |
| Folwarski et al., 2021 | Poland | ≥ 18 yr (mean: 61.9 yr) | Patients undergoing pylorus-preserving pancreatoduodenectomy | LGG powder in capsules + perioperative nutritional treatment (20) | Perioperative nutritional treatment (20) | 1 mo | $1.2x10^7$ ($6x10^6$ b.i.d.) | URTI and LRTI events (8 cases) | 99% risk reduction for pneumonia | Low sample size; low cases; broad adult age range (spanning across different life stages); low-dose LGG |
| Johnstone et al., 2021 | United States, Canada, and Saudi Arabia | ≥18 yr (mean: 59.8 yr) | Critically ill patients requiring mechanical ventilation | LGG capsules (1,318) | Placebo capsules containing microcrystalline cellulose (1,332) | 2 mo | $2x10^{10}$ | Pneumonia (607 cases) | Not significant | Large, multicenter trial; wide age range; critical illness limits generalizability |
| Damholt et al., 2022 | Denmark | 2-6 yr | Healthy children | LGG powder (309) | Placebo powder (308) | 4 mo | $1x10^9$ | URTI events (400 cases) | Not significant | Broad age range (spanning across multiple developmental stages); high events; |
| Loke et al., 2022 | Australia | 1-10 yr (5.9 yr) | Children with peanut allergy receiving oral immunotherapy | LGG + oral immunotherapy (79) | Placebo + oral immunotherapy (83) | 18 mo | $2x10^{10}$ | Diarrhea, vomiting, or abdominal pain events (36 cases) | Not significant | Broad age range (spanning across multiple developmental stages); atopic condition limits generalizability |
| Rose et al., 2010 | Germany | 6-24 mo (1.3 yr) | Children with a history of atopic diseases | LGG powder in capsules (56) | Placebo capsules (46) | 6 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Wheezing duration | Not significant | Atopic condition limits generalizability |
| Rose et al., 2010 | Germany | 6-24 mo (1.3 yr) | Children with a history of atopic diseases | LGG powder in capsules (39) | Placebo capsules (17) | 6 mo | $2x10^{10}$ ($1x10^{10}$ b.i.d) | Cough duration | Not significant | Atopic condition limits generalizability |
| Swanjlung et al., 2015 | Finland | 1-5 yr | Children referred to adenotomy | LGG powder in capsules (17) | Placebo capsules containing crystalline cellulose powder (15) | 3 wk | $8\text{-}9x10^9$ | Fever, rhinitis, sore throat, or cough duration | Not significant | Low sample size; broad age range (spanning across multiple developmental stages) |

**Supplementary Table 8** The methodological quality of the included trials on respiratory outcomes.

| Study (year) | Selection bias | | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias |
|---|---|---|---|---|---|---|---|
| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | |
| Hatakka et al., 2001 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Bousvaros et al., 2005 | Low risk | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Grüber et al., 2007 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Honeycutt et al., 2007 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Kekkonen et al., 2007 | Unclear | Unclear | Low risk | Unclear | Low risk | Unclear | Unclear |
| Scalabrin et al., 2009 | Low risk | Low risk | Low risk | Unclear | Low risk | Unclear | Unclear |
| Hojsak et al., 2010 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Hojsak et al., 2010 | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Morrow et al., 2010 | Low risk | Unclear | Low risk | Low risk | Low risk | Unclear | Unclear |
| Nermes et al., 2010 | Unclear | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Davidson et al., 2011 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Kumpu et al., 2012 | Low risk | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Kumpu et al., 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Sindhu et al., 2014 | Low risk | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Kumpu et al., 2015 | Unclear | Unclear | Low risk | Unclear | Low risk | Low risk | Unclear |
| Bruzzese et al., 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Wang et al., 2018 | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear | Unclear |
| Schnadower et al., 2019 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dziechciarz et al., 2020 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Folwarski et al., 2021 | Low risk | Low risk | Unclear | Low risk | Low risk | Unclear | Unclear |
| Johnstone et al., 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Damholt et al., 2022 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Loke et al., 2022 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Rose et al., 2010 | Unclear | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear |
| Rose et al., 2010 | Unclear | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear |
| Swanjlung et al., 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |



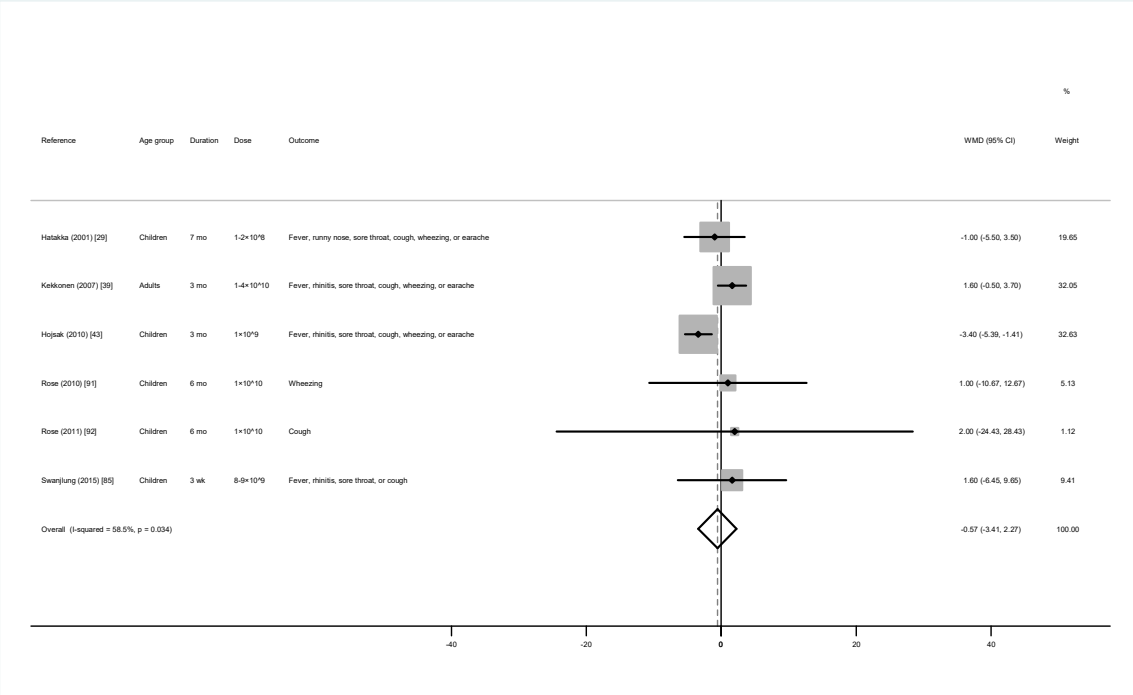

**Supplementary Figure 5** Funnel plot of the effects of Lacticaseibacillus rhamnosus GG supplementation on the risks of composite respiratory outcome (A) and respiratory infection (B)

**Supplementary Table 9** Sensitivity analyses on the effect 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** |
| Children[1] | | | | | | | | |
| Overall | 15 (4,449/1,747) | **0.88 (0.79, 0.98)** | 60.6 | — | 12 (3,261/1,557) | **0.87 (0.78, 0.98)** | 66.2 | — |
| Intervention duration | | | | | | | | |
| ≥3 months | 8 (2,348/1,406) | **0.87 (0.76, 0.99)** | 71 | | 7 (2,186/1,164) | **0.86 (0.75, 0.99)** | 73.5 | |
| <3 months | 4 (1,223/304) | 0.98 (0.87, 1.10) | 0 | 0.49† | 3 (272/158) | 0.97 (0.81, 1.16) | 24.7 | 0.50† |
| Unfixed | 3 (878/37) | 0.58 (0.12, 2.89) | 44.7 | 0.12† | 2 (803/35) | 1.04 (0.08, 13.9) | 69.5 | 0.21† |
| Daily dose | | | | | | | | |
| $\geq 10^{10}$ CFU | 6 (1,474/363) | 0.99 (0.88, 1.12) | 0 | 0.29 | 3 (286/177) | 0.99 (0.80, 1.22) | 30.3 | 0.30 |
| $<10^{10}$ CFU | 9 (2,975/1,384) | **0.83 (0.71, 0.97)** | 74.3 | | 9 (2,975/1,380) | **0.83 (0.71, 0.96)** | 72.8 | |
| Dose frequency | | | | | | | | |
| Single dose | 10 (3,172/1,481) | 0.88 (0.77, 1.01) | 71.1 | 0.86 | 9 (3,010/1,439) | 0.88 (0.76, 1.00) | 73.2 | 0.84 |
| Multiple doses | 5 (1,277/266) | 0.87 (0.74, 1.02) | 0 | | 3 (251/118) | 0.85 (0.70, 1.03) | 0 | |
| Sample size | | | | | | | | |
| ≥120 | 9 (4,023/1,605) | 0.89 (0.79, 1.01) | 72 | 0.60 | 7 (2,910/1,417) | 0.88 (0.77, 1.01) | 77.9 | 0.75 |
| <120 | 6 (426/142) | 0.84 (0.70, 1.00) | 0 | | 5 (351/140) | 0.84 (0.70, 1.01) | 0 | |
| Region | | | | | | | | |
| Europe | 10 (3,077/1,449) | **0.84 (0.73, 0.96)** | 71.8 | | 10 (3,077/1,445) | **0.84 (0.73, 0.96)** | 70.1 | |
| North America | 3 (1,087/155) | 0.96 (0.31, 3.02) | 27.7 | 0.64 | 1 (61/7) | Not pooled | — | — |
| Asia | 1 (123/105) | Not pooled | — | — | 1 (123/105) | Not pooled | — | — |
| Oceania | 1 (162/38) | Not pooled | — | — | — | Not applicable | — | — |
| Outcome subtypes | | | | | | | | |
| Respiratory infections | 12 (3,261/1,557) | **0.87 (0.78, 0.98)** | 66.2 | 0.54 | — | See overall | — | — |
| Respiratory symptoms | 4 (1,689/429) | 0.96 (0.83, 1.12) | 0 | | — | Not applicable | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Infection site | | | | | | | | |
| Upper tract | — | Not applicable | — | — | 7 (1,859/918) | **0.85 (0.72, 0.99)** | 61.5 | |
| Lower tract | — | Not applicable | — | — | 4 (957/98) | 1.01 (0.69, 1.47) | 0 | 0.47‖ |
| Any site | — | Not applicable | — | — | 8 (2,327/1,006) | **0.80 (0.66, 0.97)** | 78.8 | 0.74‖ |
| Adults[II] | | | | | | | | |
| Overall | 8 (2,670/913) | 0.80 (0.64, 1.01) | 71.5 | — | 6 (2,603/781) | 0.81 (0.58, 1.11) | 70.2 | — |
| Intervention duration | | | | | | | | |
| ≥3 months | 2 (337/183) | 0.88 (0.48, 1.62) | 86 | | 2 (337/93) | 0.96 (0.52, 1.76) | 57.9 | |
| <3 months | 4 (146/82) | 0.76 (0.54, 1.08) | 47.6 | —⁞ | 2 (79/40) | 0.74 (0.35, 1.57) | 84.8 | —⁞ |
| Unfixed | 2 (2,187/648) | 0.74 (0.35, 1.57) | 84.8 | —⁞ | 2 (2,187/648) | 0.74 (0.35, 1.57) | 84.8 | —⁞ |
| Daily dose | | | | | | | | |
| $\geq 10^{10}$ CFU | 5 (2,445/832) | 0.89 (0.70, 1.13) | 71.6 | —⁞ | 3 (2,378/700) | 1.04 (0.85, 1.27) | 16 | —⁞ |
| $<10^{10}$ CFU | 3 (225/81) | 0.50 (0.23, 1.10) | 74.6 | | 3 (225/81) | 0.50 (0.23, 1,10) | 74.6 | |
| Dose frequency | | | | | | | | |
| Single dose | 3 (2,108/646) | 0.99 (0.86, 1.14) | 0 | —⁞ | 2 (2,080/639) | 0.96 (0.77, 1.20) | 44.3 | —⁞ |
| Multiple doses | 5 (562/267) | 0.72 (0.51, 1.01) | 73.8 | | 4 (523/142) | 0.59 (0.28, 1.25) | 77.9 | |
| Sample size | | | | | | | | |
| ≥120 | 4 (2,524/831) | 0.83 (0.58, 1.17) | 83.2 | —⁞ | 4 (2,524/741) | 0.86 (0.60, 1.24) | 67 | —⁞ |
| <120 | 4 (146/82) | 0.76 (0.54, 1.08) | 47.6 | | 2 (79/40) | 0.26 (0.02, 3.82) | 82.4 | |
| Region | | | | | | | | |
| Europe | 4 (248/105) | 0.83 (0.47, 1.46) | 66.1 | —⁞ | 3 (220/98) | 0.80 (0.41, 1.56) | 77.4 | —⁞ |
| North America[a] | 4 (2,422/808) | 0.76 (0.58, 1.01) | 80.4 | | 3 (2,383/683) | 0.73 (0.43, 1.25) | 74.5 | |
| Outcome subtypes | | | | | | | | |
| Respiratory infections | 6 (2,603/781) | 0.81 (0.58, 1.11) | 70.2 | —⁞ | — | See overall | — | — |
| Respiratory symptoms | 3 (263/132) | **0.81 (0.67, 0.98)** | 0 | | — | Not applicable | — | — |

Bold numbers indicate statistically significant P <0.05
[I]All analyses performed by excluding trials in adults
[II]All analyses performed by excluding trials in children
*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.
†Trials with intervention duration of ≥3 months as a reference group
‖Upper tract as a reference group
⁞Meta-regression analyses were not performed due to limited number of trials (i.e., n ≤10)
CI confidence interval; RR relative risk




**Supplementary Figure 6** The effect of *Lacticaseibacillus rhamnosus* GG supplementation on respiratory symptom duration.