Lactobacillus rhamnosus GG: A Review of Clinical Use and Efficacy

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Abstract

Oral Lactobacillus rhamnosus GG (LGG) supplementation is generally recognised as a safe form of supplementation, which acts as an immunomodulator, an antimicrobial, and aids cell growth and proliferation. The aim of this review was to determine diseases where oral LGG supplementation has been indicated; and assess safety, colonisation, mechanisms of action and efficacy, and provide therapeutic recommendations. LGG following supplementation can successfully colonise the gut and other areas of the body owing to the expression of unique morphological features known as pili. Twenty-two disease areas were identified where LGG supplementation has been used, to determine effects. However, small study sizes, the use of multispecies probiotics and adjuvant therapies all meant that strong evidence for the use of LGG was lacking in several disease areas. Despite this, LGG was shown to be of benefit in the reduction of risk of developing attention-deficit hyperactivity disorder and gestational diabetes mellitus, in the prevention of allergies and dental caries, for improving immune reactions following vaccines, and for the management of diarrhoea associated with cancer treatments and antibiotic use.

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Introduction

Probiotics are defined as live microbes, which when administered in adequate amounts confer benefits to the host.¹ For this to occur, probiotics need to be safe, alive, of human origin and capable of surviving the pH of the gut.² Several different bacteria are used as probiotics, but species from the genera Lactobacillus and Bifidobacterium have been well researched and are believed to provide many health benefits.³⁴⁵⁶

Amongst the most well-researched strains of probiotics is *Lactobacillus rhamnosus* GG (LGG). Its health benefits are thought to derive from its superior ability to colonise the gastrointestinal (GI) tract, outcompeting and producing antimicrobials to prevent pathogenic bacterial colonisation.⁷ LGG may also promote GI barrier protection and healing through cell growth and proliferation,⁸⁹ and act as an immune effector both locally and systemically.¹⁰ Based on the mechanisms of action, clinical trials in humans have been extensive, showing benefits in several disease areas.

This review paper aims to determine the disease areas where the use of LGG as an oral probiotic has been indicated, and review the clinical data on efficacy and safety with a view to making therapy recommendations. Data on the mechanistic actions of LGG will also be briefly reviewed. Randomised-controlled trials (RCTs) will dominate this review, as the beneficial effects of probiotics seem to be strain specific;¹¹ thus, pooling data in large meta-analyses and systematic reviews with different strains may result in misleading conclusions. Where LGG alone has been examined, these will be included.

Colonisation and adhesion

The success of probiotic supplementation relies upon the ability of the microbiota to colonise areas of the body, such as the GI tract. In comparison to other *Lactobacillus* strains, LGG has high adherence to human intestinal mucus glycoproteins⁷ and, in adults, supplementation has indicated that it may survive for at least 1 week in the GI tract¹² (Figure 1). Amongst newborns and infants, a reduced intrinsic GI microbiome may ensure that LGG colonises the GI tract more readily, and it has been detected in faeces up to 2 weeks after administration, without affecting the establishment of a normal GI microbiome.¹³

![Image 1: LGG has superior mucus adherence](image1.png)

**Figure 1: Lactobacillus rhamnosus** GG (LGG) has superior adherence to mucus glycoproteins when compared with other probiotic strains, including a closely related strain of *L. rhamnosus* (LC705). In this study, radioactively labelled bacteria were allowed to adhere to isolated human intestinal mucus. The adhesion ratio (%) was determined by comparing radioactivity of bacteria added to the radioactivity of bound bacteria after washing.

Successful colonisation of LGG, compared with other *Lactobacillus* species, may be down to certain morphological features. Comparative genomic analysis with *Lactobacillus rhamnosus* LC705 has revealed the presence of a DNA sequence,
known as the *spaCBA* gene, resulting in pili-like appendages that run along the entirety of the LGG microbe, the inhibition of which lowers adhesion to the GI tract\(^{14}\) (Figure 2). Differing conditions have been shown to promote or suppress the expression of the pili phenotype in other microbiota strains;\(^{15}\) however, when exposed to different conditions such as low pH, the pili of LGG are still expressed.\(^{16}\) Interestingly, whilst LGG still expresses pili under different conditions, when present in the oral and vaginal cavities the pili are absent,\(^{16}\) which may have implications in diseases associated within these areas, such as urinary tract infections (UTIs) and dental caries.

**Image 2: Lactobacillus rhamnosus GG-specific pili**

![Image 2: Lactobacillus rhamnosus GG-specific pili](image)

Figure 2: *Lactobacillus rhamnosus* GG (LGG)-specific pili, not present on other *Lactobacillus* spp., are involved in the mechanisms of adhesion to the intestinal mucosa. In addition, the pili facilitate a close interaction between the host and the bacteria or bacteria with each other. In this image, transmission electron microscopy reveals pili on LGG cells.

Certain probiotic strains have been shown to adhere to the GI tract, preventing mucolytic bacteria from digesting the protective layer of mucus, resulting in decreased vulnerability to intestinal permeability.\(^ {17}\) Although studies have shown limited effects of LGG on intestinal permeability in patients with chronic liver conditions,\(^ {18}\) investigations into efficacy in healthy patients is warranted.

### General effects

#### Immunomodulation

The role of LGG in immunomodulation is controversial, with proteins isolated from it and its physico-chemical properties contributing to both inflammatory and anti-inflammatory actions. The pili on LGG have been implicated to have a role in immunomodulation. An *in vitro* study on LGG bred without the *spaCBA* gene, which encodes for the growth of the external pili, reported increased expression of the inflammatory cytokine interleukin (IL)-8, which was decreased with the wild-type strain.\(^ {19}\) Proteins secreted from LGG may also have an anti-inflammatory role in the immune response, and isolation of a novel soluble protein, HM0539, from LGG has been shown in colon tissue to suppress the TLR4/MyD88/NFкB inflammatory pathway.\(^ {20}\) However, overexpression of toll-like receptor (TLR)4 or myeloid differentiation primary response 88 (MyD88) did reverse this effect. The TLR4 signalling pathway may be responsible for upregulated inflammation in chronic and acute inflammatory disorders,\(^ {21,22}\) such as inflammatory bowel disease (IBD) and atherosclerosis,\(^ {23,24}\) indicating that LGG supplementation in highly inflammatory states may have a limited effect.

In contrast to its anti-inflammatory effects, effector substances such as lipoteichoic acid (LTA), found in the cell walls of certain gram-positive bacteria including LGG, may also be involved in the modulation of the immune response, with it displaying pro-inflammatory properties. Within the body, reporter cell lines are designed to monitor intracellular cell signalling pathways. LTA produced by a wild-type LGG strain has been shown to
activate the inflammatory NF-κB signalling pathway in reporter cells, a pathway that is significantly reduced when the LTA gene is removed. Removal of the LTA gene resulted in a reduced capacity to activate TLR2/6-dependent NFκB signalling in reporter cells and reduced induction of IL-8 mRNA in CACO-2 cells from the human colon, acting both locally and systemically. However, the implications of this during certain disease states and the exact role of LGG in the inflammatory and anti-inflammatory pathways still needs to be elucidated.

Supplementation of LGG in individuals with inflammatory GI diseases has shown mixed results, and is discussed later in the review.

**Cell growth and proliferation**

Proteins produced by LGG, known as Msp1 and Msp2, have been implicated in cell homeostasis through regulation of the protein kinase B (Akt) signalling pathway and inhibition of MAP kinases. In vitro studies in animal and human colon tissue have shown that Msp1 and Msp2 promoted cell growth and attenuated GI permeability in hydrogen peroxide-damaged intestinal epithelium. Msp2 has also been shown in intestinal epithelial cells, in vivo and in vitro, to inhibit cytokine-induced apoptosis, indicating a role for LGG in the protection and recovery from intestinal permeability and injury.

**Antimicrobial**

In vitro, LGG has been shown to inhibit the growth and adherence of several pathogenic bacteria belonging to the *Salmonella, Shigella, Escherichia* and *Streptococcus* species. In rabbit models, LGG has been shown to inhibit translocation of *Escherichia coli* in a dose-dependent manner. In clinical trials, a decrease in the number of children colonised with vancomycin-resistant enterococci has been reported following LGG consumption for 21 days, with increased GI *Lactobacillus* counts observed in their stead.

LGG DNA contains encodes for bacteriocins, which act like antibiotics, preventing the growth of closely related bacterial strains; however, the product of these genes has not been expressed under experimental conditions. Further experiments have reported that the antimicrobial action of LGG may be due to the production of microcin-type substances, which are small bacteriocins, mediated in part by lactic acid.

LGG may also communicate with other gut microbiota via a process known as quorum sensing (QS), resulting in cooperation for nutrients and cellular adhesion against pathogenic bacteria. The pil-like protrusions responsible for colonisation may ensure superior competitive inhibition by LGG during QS. However, further studies are required to determine the role of QS when the GI tract is faced with pathogenic bacteria.

**Clinical uses**

**Cancer**

It has been hypothesised that gut dysbiosis may promote colorectal cancer through the colonisation of pathogenic bacteria, which drives its development. Furthermore, chemotherapy treatment may alter the composition of the gut microbiota, indicating areas where probiotics may be of benefit. The use of LGG in a multispecies probiotic in combination with a prebiotic has been shown to alter several colorectal cancer biomarkers after 12 weeks. In this trial, *Bifidobacterium (P = 0.008), Lactobacillus (P = 0.021)* and interferon-gamma (IFN-γ) were all increased, with *Clostridium perfringens (P = 0.022)* and DNA damage decreased amongst 37 patients with colon cancer and 43 polypectomised patients. However, administration of the synbiotic also prevented a rise in IL-2 inflammatory cytokines. In contrast to IL-2 suppression, a second RCT on a multispecies synbiotic containing LGG, *Bifidobacterium*...
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lactis and inulin reported increased IL-2 and IFN-γ in 34 patients with colon cancer who had undergone curative resection or polypectomy. IFN-γ and IL-2 were both increased at 12 weeks compared with placebo ($P \leq 0.05$ both), but no other effects on immune factors were observed. Overall, it is difficult to conclude any specific effects of LGG from these trials as, when in combination, effects may be due to other species.

Failure of cancer treatments often occurs when severe side-effects result in a reduction or cessation of treatment. Side-effects, such as diarrhoea, can occur in as many as 30–87% of patients, with severe and potentially life-threatening (grade 3–4) episodes occurring in 20–40% of patients. Probiotics have been shown to be a safe and effective way to prevent chemotherapy-induced diarrhoea and, as monotherapy, one of the most important effects of LGG may be for its use to reduce the frequency and severity of severe diarrhoea and GI symptoms during chemotherapy treatment. In one RCT of 150 patients with colorectal cancer given LGG twice daily [1–2 × 10^{10} colony-forming units (CFU)] for 24 weeks during 5-fluorouracil chemotherapy, patients had less grade 3 or 4 diarrhoea and fewer hospitalisations due to bowel toxicity compared with a fibre supplement (22% versus 37%, $P = 0.027$; and 8% versus 22%, $P = 0.021$, respectively), resulting in decreased chemotherapy dose adjustments (21% versus 47%, $P = 0.0008$).

Perioperative administration of a multispecies probiotic containing LGG plus fructo-oligosaccharide has also been associated with reduced infection rate in postoperative patients with colorectal cancer. One trial in 91 patients undergoing surgery reported decreased infections at the incision site (2% versus 21.4%, $P = 0.002$), reduced intra-abdominal abscess ($P \leq 0.001$) and reduced incidence of pneumonia ($P \leq 0.001$), indicating a beneficial effect to complications associated with cancer treatment.

Helicobacter pylori may be the strongest known risk factor for gastric cancer, and eradication may be an effective therapy in its prevention. However, undesirable side-effects of eradication may include diarrhoea, pain, nausea and bloating, resulting in treatment cessation. During $H. \text{pylori}$ eradication, the supplementation of LGG (6 × 10^{9} CFU twice daily) has been reported to increase eradication tolerability ($P = 0.04$) due to decreased side-effects, such as diarrhoea, nausea and taste disturbances [relative risk (RR) = 0.1, 95% confidence interval (CI): 0.1–0.9; RR = 0.3, 95% CI: 0.1–0.9; RR = 0.5, 95% CI: 0.2–0.9]. Although eradication rate remained unaffected, the supplementation of LGG in individuals undergoing $H. \text{pylori}$ eradication may contribute to preventing the development of gastric cancer through increased treatment tolerability.

Results have not been as positive in other cancers, with one study in 40 patients undergoing head and neck cancer surgery reporting no impact of a multispecies synbiotic on postoperative outcomes, intestinal function or GI symptoms, indicating that the beneficial effects of LGG in cancer may be localised and specific.

It is apparent that LGG monotherapy (6 × 10^{9} CFU twice daily) has numerous benefits, including success in symptom management of $H. \text{pylori}$ treatment and reducing the risk of developing gastric cancer. For individuals undergoing chemotherapy treatment for colon cancer, LGG (1–2 × 10^{10} CFU twice daily) may be more beneficial than fibre for the reduction of diarrhoea. In combination with other probiotics and prebiotics, LGG may reduce postoperative infections and improve immune function in patients with colon cancer, which is important during a time of reduced immune function.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is characterised by abdominal pain, flatulence and irregular bowel movements, and it is estimated that 10–20% of the worldwide...
adult population suffers from this syndrome. Treatments for IBS have limited success, and newer drugs such as 5-HT₄ agonists come with cardiovascular risks, highlighting a need for treatments with limited side-effects.

In adults, it appears that several factors are involved in the pathophysiology of IBS, with mucosal large intestine low-grade inflammation and altered gut microbiota indicated. As stated earlier, in vitro studies have highlighted that LGG may have both pro-inflammatory and anti-inflammatory properties, making its role as a supplement in inflammatory diseases uncertain.

Differences in the gut microbiota between healthy subjects and sufferers of IBS have been highlighted. The administration of LGG may be able to promote colonisation and reinstate the composition of gut microbiota more associated with healthy individuals. Supplementation of a multispecies probiotic containing LGG (8–9 × 10⁹ CFU) for 6 months in 42 patients with IBS resulted in a shift towards similar quantities of bacterial 16S rDNA to those of healthy controls; however, clinical outcomes were not reported in this study. Although there was a shift in composition towards that of more healthy individuals, a gut microbiota composition that is characteristic of, or favourable for, sufferers of IBS has yet to be isolated and may be highly individual. Regardless, the administration of probiotics containing LGG may be of benefit for symptom relief in individuals with IBS. In one double-blind RCT of 49 patients with IBS, the supplementation of a multispecies probiotic (5 × 10⁹ CFU/day) containing LGG reported improvements to abdominal pain/discomfort and bloating after 4 weeks, which was attributed to alterations in the composition of the gut microbiota. Faecal analysis highlighted that LGG, B. lactis and Streptococcus thermophilus had all significantly increased in the supplemented group, although several other strains were also included in the probiotic.

IBS can be divided into subtypes, and improvements in symptoms may be highly dependent upon this, highlighting the importance of identifying the IBS type before commencing LGG supplementation. One 6-week unblinded RCT of 123 adults with IBS investigated the efficacy of LGG (6 × 10⁹ CFU/day for 6 weeks) compared with a low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet on syndrome severity, assessed using the IBS symptom severity scoring system. The results showed that LGG was as efficacious as the low-FODMAP diet, especially in the diarrhoeal (IBS-D) and mixed IBS (IBS-A) subtypes, with no improvement in those with the IBS constipation subtype. Quality of life (QoL) was also improved in those with IBS-D. Studies like this highlight the need to perform trials on dual therapy of diet changes and probiotics to further advance possible management strategies for IBS.

Children with IBS may spontaneously recover, however, for those who have persistent symptoms, the use of LGG to effectively manage IBS may also be dependent on an accurate diagnosis. Improvements to the frequency and severity of abdominal pain when supplemented with LGG may be due to improvements in the gut barrier, and may be especially pronounced in children with IBS or functional pain. In one 16-week RCT of 141 children with IBS or functional pain, LGG supplementation (6 × 10⁹ CFU/day) reduced the frequency and severity of abdominal pain (P ≤ 0.01 for both). Although it was concluded that this effect may not be unique to LGG, it is apparent that it may be of benefit. One systematic review of three RCTs with 290 children suffering from abdominal pain-related functional GI disorders concluded that a higher rate of children responded to treatment with LGG (6 × 10⁹ CFU/day to 10¹⁰ CFU/day) compared with placebo if suffering from IBS, an effect that was not evident in children without IBS. Frequency of pain was only reduced in the IBS subgroup; however, pain intensity was
reviewed amongst the whole study population. This study did not perform a statistical test for publication bias, so this cannot be ruled out and conclusions should be made with caution.

A second systematic review of 11 RCTs examining various probiotic supplements in children with functional abdominal pain disorders (FAPD) highlighted that LGG reduces the frequency and severity of abdominal pain, but only in children with IBS.\textsuperscript{25} One study of 4 weeks, which included IBS sufferers alongside those with dyspepsia and functional abdominal pain, concluded that children supplemented with $3 \times 10^9$ CFU of LGG twice daily were more likely to have improved pain frequency but not pain severity,\textsuperscript{59} further supporting the need to identify IBS for LGG supplementation to be of benefit to symptoms.

\textit{In vitro} studies have highlighted that LGG may have both pro-inflammatory and anti-inflammatory properties, and have a limited effect in inflammatory conditions. However, supplementation studies of the use of LGG to relieve symptoms of IBS in adults may be more positive, and dependent upon its use for the IBS-D and IBS-A subtypes, although this is based on data from studies using multispecies rather than LGG alone. Its use in children may be of benefit for the management of pain symptoms.

\textbf{Diarrhoea}

Diarrhoea is a leading cause of childhood mortality worldwide and is the second leading cause of childhood deaths.\textsuperscript{60} The use of probiotics and LGG for the prevention and treatment of diarrhoea has been extensively researched, with varying success. One large RCT of 943 children with moderate-to-severe gastroenteritis reported that administration of a short 5-day course of LGG $1 \times 10^{10}$ CFU twice daily was no more effective than placebo at decreasing the duration of all-cause diarrhoea (median LGG 49.7 hours versus 50.9 hours, $P = 0.26$).\textsuperscript{61}

Despite negative outcomes in all-cause diarrhoea, the understanding of the mechanisms through which LGG interacts with the host may indicate specific types of diarrhoea where supplementation may have greater success. Antibiotic-associated diarrhoea (AAD) may result from dysbiosis of the host’s gut bacteria.\textsuperscript{62} LGG acts through several mechanisms to potentially prevent dysbiosis or restore normal bacterial flora resulting from antibiotic administration, such as competitive exclusion of pathogens,\textsuperscript{63} modulation of the immune system,\textsuperscript{64} and through outcompeting less acid-tolerant bacteria as LGG produces lactic acid.\textsuperscript{65}

The prevention of gut microbiota changes associated with antibiotic use has been shown in one RCT of 231 school-aged children.\textsuperscript{65} In this trial, children given $10^6$ CFU/ml LGG in 400 ml of milk long term reported changes in several gut bacteria, with especially increased abundance of the \textit{Lactobacillus} spp. ($P < 0.0001$).

LGG for the reduction of risk of AAD has been extensively researched, and it may be important for the prevention of this disease and to provide new treatment options when antibiotics are prescribed. One meta-analysis of 12 RCTs and 1499 participants reported that, compared with placebo or no treatment, LGG was associated with a reduced risk of AAD (22.4% to 12.3%, $RR = 0.49$, 95% CI: 0.29–0.83), resulting in a number needed to treat (NNT) of 9.\textsuperscript{66} LGG may also be one of the most effective probiotics for the prevention of AAD, and a meta-analysis of 32 RCTs has reported that LGG was superior to seven single or multispecies probiotics for the prevention of AAD ($RR$ versus placebo = 0.30, 95% CI: 0.16–0.5).\textsuperscript{67} Dosages of at least $2 \times 10^9$ CFU were recommended.

Although evidence exists for the use of LGG with AAD, other causes of diarrhoea have reported mixed results. As previously discussed, \textit{in vitro} studies have indicated the ability of LGG to prevent the adherence and
viability of several gut pathogens. Amongst these, Clostridium spp. have been shown to be inhibited in vitro through the production of a bactericide that resembles microcin. However, in vivo studies in children have not been as positive. One meta-analysis of 20 RCTs concluded that the use of LGG reduced the risk of AAD from 23% to 9.6% (RR = 0.48, 95% CI: 0.26–0.89); however, it found no effect on the risk of Clostridium difficile-associated diarrhoea (RR = 0.95, 95% CI: 0.06–14.85). It should be noted that the results on C. difficile were based on only one RCT, and this warrants more research.

Studies on children with rotavirus-associated diarrhoea, which is the leading cause of vaccine-preventable diarrhoea, have been more positive. One meta-analysis of 19 RCTs concluded that, compared with control, the use of high-dose LGG (10⁸ CFU/day) in children with rotavirus-positive diarrhoea reduced the duration [mean difference (MD) −31.05 hours, 95% CI: −50.31, −11.80] and frequency of diarrhoea episodes (MD −1.08, 95% CI: −1.87, −0.28). This trial also looked at children with acute diarrhoea caused by a mixture of rotavirus, bacterial pathogens and norovirus and, in contrast to Schnadower et al. (2018), high-dose LGG reduced the duration of diarrhoea episodes (MD −15.83 hours, 95% CI: −20.68, −10.98), but only in those who had suffered from diarrhoea for less than 3 days at enrolment, indicating that earlier treatment at higher doses may have more success.

Dose-dependent effects of LGG supplementation on rotavirus-associated diarrhoea are also apparent. One open-label RCT in 23 children with rotavirus-associated diarrhoea showed no changes in faecal rotavirus concentrations when supplemented with low-dose LGG 2 × 10⁸ CFU/day (36.1 × 10⁵ particles/ml versus 73.5 × 10⁵ particles/ml, P = 0.895), but at a high dose of 6 × 10⁸ CFU/day concentrations were reduced (64.2 × 10⁵ particles/ml versus 9.0 × 10⁵ particles/ml, P = 0.012). Although rotavirus shedding and not symptoms were assessed in this trial, it is indicative of disease severity. LGG may also aid recovery from rotavirus infection, with both intestinal permeability and immunoglobulin antibodies to rotavirus improved following LGG supplementation.

Large, short-term trials for the treatment of all-cause diarrhoea have shown little improvements with the administration of LGG. Understanding the type of diarrhoea may result in a more targeted and successful approach. The use of LGG at a dose of at least 6 × 10⁸ CFU during a course of antibiotics may prevent AAD, and early high-dose treatment during rotavirus-associated diarrhoea may decrease the duration of disease, the frequency of diarrhoea episodes and aid recovery.

**Inflammatory bowel disease**

IBD is an umbrella term for a number of different diseases, which includes Crohn’s disease and ulcerative colitis. As the name suggests, inflammation plays a major role in its development, and its aetiology is thought to be a combination of both genetic and lifestyle factors. The gut microbiota may also play a major role in the pathogenesis of IBD, and in individuals with Crohn’s disease, gut dysbiosis has been reported with an increased growth of E. coli and a reduction in the bacterial phyla Firmicutes, of which LGG is a member.

As previously discussed, LGG may have pro-inflammatory properties, and limited effects in inflammatory GI diseases such as IBD. Remission of Crohn’s disease, endoscopic recurrences and relapse times have all been shown to remain unaffected by LGG supplementation. One systematic review and meta-analysis of 41 studies, two of which were in LGG, reported no difference in endoscopic recurrences when supplemented with LGG, compared with placebo (0.93; 95% CI: 0.63, 1.38). In a second meta-analysis of six RCTs, four of which were in LGG, the supplementation of LGG was concluded to increase the relapse
rate of individuals with Crohn’s disease. In this trial of 359 individuals, placebo showed a greater benefit on clinical relapse rates in adults (RR = 1.85, 95% CI: 1.00−3.41) and children (RR = 1.68, 95% CI: 1.07−2.64) compared with LGG, with little heterogeneity between the studies (P = 0.71, I² = 0%).

Studies on the use of LGG in children have also not been efficacious. LGG in combination with standard Crohn’s disease treatment has shown marginally shorter time periods between relapses. One RCT with a 2-year follow-up in 75 children who were in a period of inactive Crohn’s disease reported a non-significant shorter time between the median time to relapse in those treated with LGG compared with those on placebo (9.8 months versus 11 months, P = 0.24). There is a possibility that concomitant therapies may be masking the effect of LGG; however, in combination with the previously reviewed studies that have shown no effect of monotherapy, it would suggest that this is not the case.

When LGG is combined with other gut bacteria strains, anti-inflammatory actions have been observed; however, given the previous in vitro and in vivo research, it is likely that the extent of anti-inflammatory effects is due to the gut bacteria strain it has been combined with. One open-label parallel study reported an anti-inflammatory effect with a combination of LGG GR-1 strain and Lactobacillus reuteri in a yoghurt supplement given to 20 participants with Crohn’s disease and ulcerative colitis. In this study, LGG dosage of 2 × 10⁷ CFU/ml and 1 × 10³ CFU/ml and L. reuteri were associated with increased levels of CD4⁺ CD25high T-cells (P = 0.007), which are involved in immune regulation, and decreased inflammatory cytokines, tumour necrosis factor-alpha (TNF-α) and IL-12 compared with healthy controls. However, the anti-inflammatory effects observed may be due to the presence of L. reuteri. Given the in vitro evidence and the supplemental studies, there is very minimal evidence for the use of LGG in inactive Crohn’s disease for endoscopic recurrences, and it may even be detrimental to overall relapse rates. Individuals with Crohn’s disease have been reported to have antibacterial reactivity and a loss of tolerance for their own enteric flora and, given the results above showing low colonisation of LGG in the guts of those with Crohn’s disease, could indicate a need to increase supplemental doses above those already tested. However, this would raise safety concerns and, given the lack of dose-response trials, this is an area that requires more research.

**Body weight**

The relationship between body weight, diet and gut microbiota is complex, with each component influencing the other. The involvement of the gut microbiota in the development of metabolic disorders is thought to involve nutrient and lipid metabolism, and hormone and immune modulation. In animal models, diets supplemented with LGG had hypercholesterolaemic effects and caused increased satiety, with increased peptide YY production; however, mechanisms are still being debated.

The role of the two major phyla, Firmicutes, to which LGG belongs, and Bacteroidetes in obesity and weight loss has been extensively researched and remains controversial. Observations in obese children and overweight/obese women with metabolic syndrome have shown an increased Firmicutes to Bacteroidetes ratio, compared with their healthy counterparts. Furthermore, a reduction in the Firmicutes to Bacteroidetes ratio has been observed in obese individuals following weight loss. The controversy over the role of Firmicutes and LGG occurs when looking at supplementation. Studies would suggest
that LGG has little effect on weight gain, as two trials of LGG with differing gut bacteria species have shown differing results. One RCT reported no significant effect of a combination supplement containing $6.5 \times 10^9$ CFU/day LGG and *B. lactis* on the prevention of excessive gestational weight gain in 230 obese pregnant women (probiotics versus placebo, RR = 1.14, 95% CI: 0.99−1.31). However, in contrast, one RCT showed that supplementation with a multispecies probiotic of *Bifidobacterium animalis* and LGG at $1 \times 10^9$ CFU/day in 411 obese and overweight pregnant women resulted in lower maternal weight gain compared with placebo. It could be concluded from these two studies that the presence of LGG is having no effect on weight loss or gain, and it is the other species of gut bacteria that may be exerting its effects.

Underlying pathophysiology during obesity may also remain unaffected by LGG supplementation. One RCT sub-study of 26 healthy adults reported that LGG supplementation of $6.2 \times 10^7$ CFU/day for 3 weeks in a milk-based fruit drink resulted in changes in serum global lipid profiles, with decreased lysophosphatidylcholines ($P \leq 0.05$), sphingomyelins ($P \leq 0.001$) and several glyco- phosphatidylcholines ($P \leq 0.05$), which may be involved in the pathophysiology of atherosclerosis. It should also be noted that triglycerides were increased and when the trial adjusted their statistics to allow multiple hypothesis analysis, no changes were observed in global lipidomic profiles.

The effect of LGG in weight loss remains controversial. Observational studies have outlined a negative effect of the Firmicutes phyla on weight loss, but supplemental trials of specific strains are not straightforward. As effects may be species dependent, it cannot be discounted that positive trials of supplementing multispecies probiotics containing LGG were due to a symbiotic effect of the two strains or due to the *Bifidobacterium* strain present in the supplement. It should be noted that caloric intake and exercise were not measured in these trials, which could affect outcomes.

### Liver disease

The gut–liver axis is now a well-recognised relationship that is thought to interact through the mesenteric portal vein. The pathological progression of non-alcoholic fatty liver disease (NAFLD) development is thought to involve inflammation and lipotoxicity. Thus, targeting the gut–liver axis to treat NAFLD may be promising for the treatment of this multifactorial disease.

The use of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as clinical markers of liver damage is well established. However, an understanding of liver disease is not limited to liver function, but also considers the presence of small intestinal bacterial overgrowth (SIBO) and intestinal permeability, as endotoxaemia may contribute to reduced life expectancy in individuals with liver cirrhosis. The use of probiotics to improve SIBO is thought to occur from successful colonisation of the small intestine, which prevents microbial translocation. However, in one RCT of 53 patients with chronic liver disease, successful colonisation of LGG and improved SIBO did not translate into improved intestinal permeability and liver function after 4 weeks. This study used a multispecies probiotic of six different strains, including LGG, and reported increased LGG in faeces ($P \leq 0.001$) and improved SIBO ($P \leq 0.05$), but only marginally improved intestinal permeability and no changes to liver chemistry. Short treatment duration and the study population could be responsible for observations.

In comparison, longer studies on LGG monotherapy in children have reported improved liver chemistry. Compared with placebo, 8 weeks of LGG supplementation ($1.2 \times 10^{10}$ CFU) in 20 children with NAFLD has been associated with decreased ALT ($P \leq 0.03$) and anti-peptidoglycan-polysaccharide
antibodies ($P = 0.03$),
which are polymers from the cell wall of bacteria that may contribute to inflammation in certain chronic inflammatory diseases.$^{100}$ Differences in dosages between the studies may account for conflicting results; however, the dosage was not disclosed in the previous study. The previous study may also have been too short to observe differences, or the use of a multispecies probiotic may be masking the effects of LGG. The small number of study participants in the monotherapy study may have also been giving a false-positive.

The research surrounding the use of LGG for the improvement of liver function and SIBO is still in its infancy. The use of LGG for the improvement of liver function in paediatric liver disease is promising at a dose of at least $1.2 \times 10^{10}$ CFU/day. In adults, more large-scale RCTs are required, as there is yet no compelling evidence for LGG efficacy in NAFLD, despite promising results for improving SIBO when given in combination with other species. More research is also required in this area, especially with regards to those with severe disease, as the use of probiotics in immunocompromised individuals has raised some concerns.$^{18}$

**Insulin resistance and type 2 diabetes**

Gut dysbiosis has been linked to insulin resistance (IR) and type 2 diabetes (T2D). In contrast to studies on individuals with obesity, individuals with T2D show compositional changes of the intestinal microbiota, which include decreased Firmicutes, resulting in an increased Bacteroidetes to Firmicutes ratio within the intestinal microbiota.$^{101}$ Despite this, studies on individuals with T2D have reported increased total *Lactobacillus* anaerobes, with pronounced levels of *L. reuteri* and *Lactobacillus plantarum*.$^{102}$ However, the role of native LGG in those with T2D is unclear.

As previously discussed, gut dysbiosis and the development of intestinal permeability may lead to endotoxaemia and systemic inflammation, and this may contribute to the pathogenesis of IR and T2D. The effects of probiotics in T2D may be through the production of glutathione, decreasing inflammation and oxidative stress. Supplementation of a multispecies probiotic containing LGG for 8 weeks in 54 individuals with T2D was shown in one trial to prevent a rise in fasting plasma glucose, decrease blood markers of inflammation ($-777.57$ ng/ml versus $+878.72$ ng/ml, $P = 0.02$) and increase the antioxidant glutathione compared with placebo ($240.63$ µmol/l versus $-33.46$ µmol/l, $P = 0.03$). Measures of IR were increased in both groups; however, less so in the probiotic group (+$2.38$ versus $+0.78$, $P = 0.03$).

As with many studies in multispecies probiotics, it is important to understand the role of LGG to rule out influences from other species. Studies on streptozocin-induced diabetic rats reported improved glucose tolerance and IR after 4 weeks consumption of LGG.$^{104}$ However, animal studies on LGG dominate, and trials in humans with T2D are lacking. Amongst 200 healthy individuals, LGG supplementation of $1 \times 10^9$ CFU for 90 days was shown in one trial to help maintain glycaemic control.$^{105}$ Compared with placebo, where glycated haemoglobin (HbA1c) increased over the 90 days, the LGG-supplemented group reported sustained HbA1c levels ($P = 0.005$ between-group comparison), indicating possible attenuation of T2D development in healthy adults.

Results from the study above indicate that supplementation of LGG may be of benefit in slowing the development of T2D, an effect that was also observed in gestational diabetes.$^{106}$ In this trial of 256 pregnant women with normal glycaemic levels, those supplemented with multispecies LGG + *B. lactis* in combination with dietary advice reported improved blood glucose control during pregnancy and a reduced risk of elevated glucose concentration compared with placebo [odds ratio (OR) 0.31,
95% CI: 0.12, 0.78, \( P = 0.028 \). These effects were sustained 12 months post-partum; however, dosages were not stated in the trial and the role of a single-strain LGG probiotic is unclear. Moreover, a potential effect of the dietary changes cannot be discounted. In contrast, a multispecies probiotic of LGG + \( B. \) \textit{animalis} (1 \times 10^9 \text{ CFU/day}) discussed previously in this review failed to prevent gestational diabetes.\(^9\) Taken in tandem, these studies would suggest that effects on glycaemic control in pregnancy could be dependent upon dietary changes.

The use of 1 \times 10^9 \text{ CFU LGG} as monotherapy or as part of a multispecies probiotic to slow the pathophysiological continuum from IR to T2D in healthy individuals may be of benefit. The studies on gestational diabetes mellitus (GDM) would suggest little effect of LGG, and that dietary changes were the driving factor.

**Cystic fibrosis**

Intestinal inflammation is a predominant feature in adults and children with cystic fibrosis (CF), with levels similar to individuals with IBD.\(^{107,108}\) Improvements to intestinal inflammation in patients with CF have been reported following probiotics\(^{109}\) and LGG supplementation as a monotherapy. The restoration of disrupted intestinal microbiota and improvements to intestinal inflammation in children with CF has been reported following supplementation with LGG.\(^{108,110}\) In one RCT, supplementation of 6 \times 10^9 \text{ CFU/day LGG} resulted in reduced faecal calprotectin (CLP), which is indicative of intestinal inflammation, in the GI tract of 22 children with CF (184 ± 146 \text{ µg/g versus } 52 ± 46 \text{ µg/g, } P \leq 0.01).\(^{110}\) Correlations between reduced microbial richness and intestinal inflammation were also observed in this trial (\( r = 0.53, P = 0.018 \)).

Although inflammation may be improved, the effects of LGG supplementation on pulmonary exacerbations and hospital stays remain controversial. LGG supplementation of 6 \times 10^9 \text{ CFU/day} reduced pulmonary exacerbations and hospital admissions in one 6-month RCT of 43 children with CF; however, the duration of stay did not differ between the groups.\(^{11}\)

In a more recent, larger RCT in 95 children, LGG supplementation (6 \times 10^9 \text{ CFU/day}) failed to show any effect on hospitalisations (OR 1.67, 95% CI: 0.75–3.72, \( P = 0.211 \)) or exacerbations (OR 0.83, 95% CI: 0.38–1.82, \( P = 0.643 \)).\(^{11}\) In contrast to the previous trial, this trial of 95 children with CF ran for 12 months. Study design and duration may account for differences, with parallel studies enabling comparisons between treatments at the same time amongst differing individuals, whereas crossover studies negate the effects of between-patient variability. In this instance, the crossover study could eliminate differences between the participants, such as severity of disease or dietary and lifestyle differences.

The data for the use of LGG in CF mainly revolve around studies in children. Supplementation with 6 \times 10^9 \text{ CFU LGG} may reduce intestinal inflammation and restore gut microbiota eubiosis; however, the exact effects on pulmonary exacerbations remain unclear.

**Respiratory tract infections**

Removal of the adenoids has been associated with increased long-term risk for respiratory tract infections (RTIs),\(^{113}\) indicating their possible involvement in the body’s immune defence against respiratory diseases. Although largely considered a member of the gut microbiota, the importance of LGG for the immune system may be apparent from its presence in large amounts in the adenoids of children, which has been shown to increase following 3 weeks of supplementation.\(^{114}\)

However, its role in the prevention of RTIs and its ability to reduce symptoms and duration of illness remain controversial. The use of an LGG supplement (1 \times 10^9 \text{ CFU/day}) for 6 weeks in 59 adults artificially infected with human rhinovirus failed to affect viral load when compared with placebo.\(^{115}\) Furthermore, one study failed to show benefits to severity of cold symptoms of a live LGG supplement (1 \times 10^9 \text{ CFU/day})
compared with an inactivated form and placebo in 60 adults after 6 weeks. Although this study did indicate a trend towards lower occurrence and severity of cold symptoms in the active LGG group, this was not significant.

Studies in younger adults and children have shown more beneficial outcomes of LGG supplementation in RTIs. Amongst 231 healthy college students, the use of LGG (1 × 10^9 CFU/day) in combination with *B. animalis* for 12 weeks was shown to improve the severity and duration of upper RTIs (URTIs), with a 2-day shorter average infection, leading to fewer school days missed compared with placebo ($P = 0.002$). As this study was in combination with *B. animalis*, it is difficult to determine the exact effect of LGG; however, the combination therapy was shown to be of benefit.

Over-the-counter RTI medications in children under 6 years old are often avoided and discouraged due to concerns with safety and efficacy, indicating a need for alternative therapies in this cohort. Children attending day care facilities are particularly susceptible to RTIs due to factors such as increased exposure to infections and cessation of breastfeeding, which contributes to a number of childcare and workdays lost. Therefore, the use of probiotics may be of benefit. Strain-specific effects have been highlighted, with LGG reducing the duration of RTIs in children at day care, which other strains failed to do in a systematic review and meta-analysis of 15 RCTs with 5121 children ($MD = 0.78$ days, 95% CI: −1.46 to 0.09, $P = 0.022$). Interestingly, this meta-analysis reported no effect on incidence, antibiotic use or days missed from day care, which differs to an earlier systematic review and meta-analysis of four RCTs in 1805 children, which reported reduced risk of URTIs (RR = 0.62, 95% CI: 0.50–0.78, NNT = 4) and antibiotic use (RR = 0.80, 95% CI: 0.71–0.91) with LGG supplementation. Differences between the results may be due to a lack of recent data supporting LGG supplementation, or could be owing to differing trial designs and outcome measures.

In high-risk children, the supplementation of prebiotics and probiotics may reduce the risk of RTIs and rhinovirus infections. In one study of 94 preterm infants, supplementation with LGG (1 × 10^9 CFU/day for the first 30 days, and 2 × 10^9 CFU/day for a further 30 days) reduced the incidence of RTIs (RR = 0.50, 95% CI: 0.28–0.90, $P = 0.022$) and rhinovirus infections (RR = 0.49, 95% CI: 0.24–1.00, $P = 0.051$). In a second study, LGG supplementation (1 × 10^9 CFU/day) in 742 hospitalised children reduced the risk of RTIs compared with placebo, but failed to impact hospitalisation duration.

The apparent lack of efficacy of LGG in adults for the prevention of RTIs may be due to suboptimal dosages, as the trials above largely used dosages like those used in the studies on children. Dosage–response studies are warranted to investigate this. Studies on children have shown positive results for the use of LGG in reducing the duration of RTIs in those attending day care. In high-risk children, LGG may reduce the occurrence of rhinovirus infections when supplemented with at least 1 × 10^9 CFU/day for at least 2 months.

**Otitis media**

Usually considered an extension of an URTI in children, otitis media is a spectrum of diseases characterised by middle ear inflammation resulting in pain, irritability and fever. As previously discussed, the presence of LGG in tonsil and adenoid tissue is indicative of its role in the immune system and RTIs, but there are limited data on its role in otitis media. LGG has been detected in the middle ear following supplementation, but LGG may already be present in the middle ear of children with otitis media and, compared with placebo, LGG supplementation may have limited effects on children undergoing tympanostomy, which is a procedure to prevent fluid build-up in the middle ear. In one study of 309 children prone to otitis, a multispecies probiotic containing LGG supplemented (8–9 × 10^9 CFU/day) for 24 weeks failed to reduce pathogenic bacteria in the nasopharynx, or reduce
frequency and occurrence of acute otitis media. In contrast, a multispecies probiotic containing LGG supplemented for 6 months reduced the presence of human bocavirus (HBoV), which is the primary pathogen in otitis media, in 269 children prone to otitis (6.4% versus 19.0%, OR 0.25, 95% CI: 0.07–0.94, \( P = 0.039 \)); however, the effects on symptoms and otitis media were not discussed.

The presence of LGG in the middle ear may be indicative of its role in infection prevention; however, there are limited data regarding the use of LGG for the management of otitis media in children and adults. Although studies are positive for the use of LGG as part of a multispecies probiotic to reduce the presence of the virus, more studies are warranted on LGG in isolation.

**Anxiety and depression**

Anxiety and disordered gut function often coexist, with symptoms of nausea and stomach pain reported by individuals with elevated anxiety. The gut microbiota may communicate in a bi-directional manner with the brain along the gut–brain axis in a number of different ways, such as signalling through metabolites, through the enteric nervous system and the neural-immune system. Under physiological conditions, neurotransmitters such as γ-aminobutyric acid (GABA) may be synthesised and released from *Lactobacillus*. However, under pathophysiological conditions, inflammatory cytokines produced in the gut may also have the capacity to affect the brain and stimulate the release of cortisol, dysregulating the hypothalamic–pituitary–adrenal (HPA) axis leading to initiation of the stress response. Furthermore, gut dysbiosis has been implicated in mental health disorders. Therefore, modification of the gut microbiota using probiotics may hypothetically provide a novel treatment target for conditions such as anxiety and depression.

Studies on probiotics in anxiety and depression are extensive; however, they may not be translatable to the use of LGG in isolation. The inclusion of LGG in a multispecies probiotic supplemented for 6 weeks in 70 petrochemical workers showed improvements from baseline in general health (16.9 ± 1.8 versus 9.8 ± 1.9, \( P = 0.001 \)) and depression and anxiety (18.9 ± 3.2 versus 9.4 ± 4.0, \( P = 0.006 \)), and no effects were seen in the placebo group, or in any of the groups on the HPA axis, as measured by the General Health Questionnaire and the Depression Anxiety and Stress Scale. This indicates that effects may be independent of the HPA axis, or that the short study period may have been insufficient for effects on symptoms to be observed.

The use of LGG as a monotherapy may have a beneficial effect on depression in individuals following the occurrence of myocardial infarction (MI). Supplementation with LGG (1.6 × 10⁹ CFU/day) had beneficial effects on depression, oxidative stress and inflammation in individuals post-MI who had undergone percutaneous intervention (PCI). This study of 44 individuals reported that, compared with placebo, 12 weeks of supplementation with LGG decreased symptoms of depression (−5.57 versus −0.51, \( P = 0.045 \)) and increased QoL (23.6 versus 0.44, \( P = 0.023 \)). Biomarkers for inflammation and oxidative stress were also decreased in the supplementation group compared with placebo. Low-grade inflammation may contribute to the development of depression, and the mechanism of action of LGG in depression and inflammatory diseases may be through its immunomodulatory properties.

During pregnancy, physical and psychological changes can occur leading to stress and adverse outcomes in the baby. Pregnancy with obesity may increase the risk for the development of depression and anxiety compared with entering pregnancy at a normal weight and as probiotics are considered safe during pregnancy, they may hypothetically provide a treatment option. However, in practice, clinical trials on
a combination of LGG + B. lactis failed to improve the mental health of 230 obese pregnant women at 36 weeks of gestation. There were no differences between depression scores, and anxiety and physical wellbeing worsened with time.

Studies on the use of LGG in isolation in depression and anxiety are limited, and although plausible mechanisms for its use exist, further studies are warranted in this cohort of individuals. The use of LGG (1.6 × 10^9 CFU/day) for 12 weeks for the development of depression and anxiety in individuals who are post-MI is promising.

**Attention-deficit hyperactivity disorder and Asperger’s syndrome**

Attention-deficit hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder that is present in as many as 3% of children and predominantly in boys. Symptoms such as inattention and hyperactivity are hallmark symptoms of ADHD, which are frequently observed in children with Asperger’s syndrome (AS) alongside disordered emotional behaviour. As previously discussed, LGG may affect emotional behaviour via the vagus nerve and regulation of GABA in the amygdala and hippocampus areas of the brain, which may also be involved in the pathophysiology of mental health disorders.

Animal studies have indicated a possible benefit to learning and memory following LGG supplementation; however, in humans the life stage at which LGG supplementation occurs may be important for favourable outcomes. Pre-natal and post-natal factors have been implicated as risks for ADHD and AS, and intervention with LGG at both stages may impact development later in childhood. Compared with placebo, LGG supplementation (1 × 10^9 CFU/day) 4 weeks prior to and 6 months after birth reduced the risk of development of ADHD and AS in 75 children, 13 years later (17.1% versus 0%, \( P = 0.008 \)).

Studies on the use of LGG in ADHD and AS are limited; however, what does exist is promising for the use of LGG (1 × 10^9 CFU) during late pregnancy and infancy to reduce the risk of development. With such strong mechanistic links between neurodevelopmental disorders and the use of LGG, studies are warranted to further investigate possible clinical benefits.

**Urinary tract infections**

UTIs are a commonly occurring condition, which are ordinarily treated with the use of antibiotics. However, research would suggest that this practise may be detrimental, due to the development of multi-drug-resistant bacteria. *Escherichia coli* originating from the gut microbiota is thought to be the cause in the majority of cases, and in women it may colonise the vagina, transfer to the urethral opening and ascend to the bladder.

Experiments in murine models have shown that the LGG-derived effector protein, HM0539, can competitively inhibit the adhesion of *E. coli* in the GI tract. However, one pilot trial of 42 post-menopausal women indicated that although the GI tract is readily colonised by LGG, vaginal swabs show poor adhesion, with only 9.5% of women having colonisation in this area. Possibly owing to this, clinical trials on the use of probiotics for the prevention of recurrent UTIs have shown mixed results, with vaginal colonies recurrently transferring to the urethral opening. The use of *Lactobacillus spp.* was shown in one systematic review and meta-analysis of nine clinical trials to reduce the risk of recurrent UTIs in females (RR = 0.684, 95% CI: 0.438–0.929, \( P \leq 0.001 \)); however, different strains showed varying efficacy and LGG was not analysed. When administered as a monotherapy, the regular consumption of cranberry juice, but not LGG, was determined to prevent *E. coli*-derived recurrent UTIs in one 12-month RCT of 150 women. In this trial, 39% of women in the LGG group reported recurrent UTIs compared with 16% consuming cranberry juice and 20% of control. Poor colonisation of the periurethral area and consumption only
five times per week were determined to be the possible reasons for lack of efficacy. In contrast, a multispecies probiotic containing LGG in 181 children has been reported to be effective at reducing the risk of recurrent UTIs compared with placebo ($P = 0.02$); however, in individuals who did have a recurrent event, those on probiotics had a shorter duration to recurrence (3.5 months probiotic versus 6.5 months placebo, $P = 0.04$). As this study looked at multispecies probiotics, it is difficult to determine the role of LGG monotherapy in this cohort.

Amongst individuals who have had a spinal cord injury, the risk of recurrent UTIs may be higher due to physiological alterations in the urogenital system.

The daily use of LGG in combination with *Bifidobacterium* BB12 ($7 \times 10^9$ CFU) in a 6-month RCT failed to show efficacy in preventing UTIs in 207 people with spinal cord injury compared with placebo. It would appear that only through intravesical administration does LGG improve symptoms of UTIs.

There appears to be little benefit to women in the use of LGG for the prevention of recurrent UTIs possibly due to poor colonisation in the vaginal area in the absence of the pili that aid adhesion in the GI tract, and continual transfer to the urinary tract. Amongst individuals with recurrent UTIs due to spinal cord injury, the use of LGG may only be of benefit to symptoms through intravesical administration. More studies are required in children to determine the role of LGG as a monotherapy, as its inclusion in a multispecies probiotic is promising for the prevention of UTIs.

**Infant health**

The gut microbiome begins to develop immediately after birth, and can be determined by mode of delivery and feeding. Infants born vaginally are typically colonised with beneficial bacteria from the mother’s vaginal canal, and those born through Caesarean-section (C-section), from the mother’s skin. Individuals born via C-section may have a higher risk of developing several metabolic and immune disorders later in life, possibly due to a lack of *Escherichia-Shigella* and *Bacteroides* species, and lower bacterial richness and diversity.

Colonisation of pathogenic bacteria early in life has been shown to contribute to poorer health outcomes later in life. However, despite the ability of LGG to competitively inhibit pathogenic bacteria and act as an antimicrobial in adults, results have been mixed in children, with one RCT reporting no effect of 42 weeks of LGG supplementation on the colonisation of *Staphylococci* in 60 pre-term infants, despite rapid colonisation of LGG. In addition, no effects were seen on growth rate or length of hospitalisation in this trial. The analysis of only one pathogenic bacteria may not be sufficient, and other strains may need to be analysed to understand the exact effects. In contrast, benefits to height and weight of babies at 12 months have been observed following *in utero* LGG supplementation. In this RCT, 208 healthy pregnant women were given LGG ($7 \times 10^8$ CFU/day) in combination with *B. lactis* ($7 \times 10^8$ CFU/day), resulting in increased baby weight and height at 12 months compared with placebo. Furthermore, one 6-month RCT of 120 healthy infants fed with LGG (dosage not stated) in supplemented formula have reported better LGG colonisation (91% versus 76%, $P \leq 0.05$), which led to better growth compared with formula milk without LGG. Higher than normal defecation was reported in the LGG-supplemented group; however, this was not considered to be diarrhoea or detrimental to health. Differing trial durations, stages of supplementation and follow-up times could be responsible for differences between the outcomes, with at least 6 months of treatment required to show benefits.
follow-up of a RCT, concluding that pre-natal multispecies probiotic use may be a safe and cost-effective way of preventing metabolic disease in offspring. In this study, the use of LGG and \textit{B. lactis} (1 × 10^{10} \text{ CFU/day}) in combination with dietary advice in 256 pregnant women from the first trimester to cessation of breastfeeding reduced the frequency of GDM compared with dietary advice alone \((P \leq 0.003)\). In those who did develop GDM, smaller birth weight of babies was observed. With birth size being a risk factor for obesity in later life, LGG supplementation may have an impact \textit{in utero} on later development of non-communicable diseases.

Supplementing LGG \textit{in utero} or during infancy for improved outcomes at all stages of life is apparent. Although supplementation for improved growth rates in babies is controversial, the results would suggest that 6 months of supplementation either starting \textit{in utero} or during infancy may be required at doses of at least 7 × 10^{8} \text{ CFU/day}, and potentially in combination with \textit{B. lactis}. Supplementing LGG (1 × 10^{9} \text{ CFU}) in combination with \textit{B. lactis} (1 × 10^{9} \text{ CFU}) during pregnancy may have benefits to both the mother and child in preventing the development of GDM and non-communicable diseases in later life.

**Infantile colic**

Although not life threatening, the impact of a child with colic extends to parental distress, anxiety and depression, and may be associated with the development of disorders such as allergic disease, migraine and GI disorders later in life. Thus, the reduction in the time a child with colic spends crying may have huge neuropsychological implications. One recent RCT of 45 colicky breastfed infants showed that a high dose of LGG (5 × 10^{9} \text{ CFU/day}) in combination with elimination of cow’s milk from the mother’s diet reduced crying time and GI inflammation, with no adverse events reported even at this high dose. However, a lower-dose LGG supplementation (1 × 10^{9} \text{ CFU/day}) for 6 months in an RCT of 184 infants was shown not to prevent colic based on symptoms or physician’s diagnosis when compared with control. This finding was supported in an earlier pilot study of 17 breastfed infants given LGG (4.5 × 10^{9} \text{ CFU/day}) in combination with behavioural support and cow’s milk elimination by the mother. LGG supplementation did not affect crying time or GI inflammation, but crying occurrences were decreased. Differing dosages used in the trials above may account for discrepancies between the results, with a higher dosage being more successful. Elimination of cow’s milk may also account for discrepancies.

LGG when included as part of a multispecies regimen has shown more consistent success. When included as part of a nine-strain multispecies synbiotic, a recent RCT of 4 weeks in 17 breastfed infants reported efficacy, with a decrease in the number of crying days and average crying duration when compared with Simethicone, which is used to relieve gas and GI discomfort. Although this trial was small, these findings were also supported in a larger, earlier RCT of 50 breastfed infants with higher treatment success and higher symptom resolution when given a seven-species synbiotic containing LGG (1 × 10^{9} \text{ CFU/day}).

The use of high-dose LGG supplementation as monotherapy (5 × 10^{9} \text{ CFU/day}) in combination with cow’s milk elimination has been shown to be efficacious in colic to reduce crying time and GI inflammation. Furthermore, when included as part of a multispecies synbiotic regimen, LGG may be of benefit to infants with colic to improve symptoms and crying. However, there are no studies to date showing efficacy of the use of LGG as a monotherapy.

**Human immunodeficiency virus**

As with colorectal cancer, the success of treatments for human immunodeficiency virus (HIV) is often dependent upon their tolerability. Diarrhoea is a common side-effect of anti-retroviral treatments and, in addition, patients
who are immunocompromised may be at a higher risk of microbe-associated diarrhoea. However, unlike patients with colorectal cancer, 17 patients infected with HIV who had suffered from diarrhoea for more than 1 month showed little improvement to diarrhoea or GI symptoms following LGG supplementation twice daily (1–5 × 10^{10} CFU) for 2 weeks compared with placebo. There were no differences in faecal counts of LGG between the two treatments, indicating poor colonisation following supplementation.

Previous trials have shown lower faecal Lactobacillus cultures in patients infected with HIV compared with healthy individuals, indicating a possible need for increased dosages. Further trials are warranted, as the use of LGG in other cohorts of patients for the prevention and treatment of diarrhoea has been of benefit.

**Acne**

The pathogenesis of acne involves several factors, including inflammation and alterations of insulin signalling. Systemic supplementation of probiotics to improve the insulin signalling pathway has been discussed previously, and hypothetically LGG could be used to improve acne. Improvements to the expression of genes involved in the insulin signalling pathway of individuals with acne have been reported with supplementation of *L. rhamnosus* SPI (3 × 10^{9} CFU/day) for 12 weeks. Subjects (*n* = 10) in the supplementary arm reported reductions in IGF-1 gene expression (*P* ≤ 0.001) and increased FOXO1 gene expression (*P* ≤ 0.001) from baseline, with no changes observed in the placebo arm (*n* = 10). This resulted in physician-rated improvements to skin appearance of acne in the *L. rhamnosus* SPI group compared with the placebo group (OR 28.4, 95% CI: 2.2–411.1, *P* ≤ 0.05). Although the study states that the strain used is also known as LGG, there is very little research to confirm this; however, based on the previous research on LGG and IR, it would appear it may have similar actions. It should also be noted that the study was only completed in Caucasian subjects, and translatability into the skin of other races is unknown. In addition, small sample sizes and the pilot nature of the study warrant further research.

Based on a single, small pilot study, the use of *L. rhamnosus* SPI (3 × 10^{9} CFU/day) for at least 12 weeks for the improvement of acne through modulation of the insulin signalling pathway is promising; however, more research is needed in larger higher-powered studies to confirm effects. Studies on the genetic sequencing of *L. rhamnosus* SPI and its relationship to LGG or further research on LGG as the test probiotic are also warranted.

**Allergy**

Allergy development is thought to involve both genetic and environmental factors. Dysbiosis and reduced diversity of the infant gut microbiome are thought to be included in the pathogenesis of allergic disease in children, due to factors such as antibiotic use *in utero* and birth by C-section. However, effects may be ameliorated using probiotics. One RCT on the use of a multispecies probiotic containing LGG (5 × 10^{9} CFU/day) during pregnancy, breastfeeding and infancy, reported altered effects of antibiotics and C-section birth on gut dysbiosis, increasing *Bifidobacteria* and reducing pathogenic *Proteobacteria* and *Clostridia*, indicating that the use of probiotic supplementation during infancy may help to restore eubiosis.

Observational studies have indicated that the involvement of *Lactobacillus* species may be of particular importance in the development of allergies. The presence of LGG, *Lactobacillus casei* and *Lactobacillus paracasei* early in life is associated with lower prevalence of allergic disease in childhood, and there may be a lower presence of *Lactobacillus* in children with a genetic predisposition, due to one or more parent having allergic disease. The use of LGG supplementation to decrease the risk of allergy development has also been studied. Benefits to the prevalence of allergic...
disease later in life were apparent in a follow-up of patients from four separate RCTs on 303 pre-term children given different strains of probiotic. Children who were given LGG perinatally had a decreased prevalence of allergic disease compared with children given placebo at the 2-year follow-up (OR 0.62, 95% CI: 0.38–0.99, \( P = 0.047 \)). Treatment durations from the four included trials ranged from 3 to 6 months, and dosages from \( 1 \times 10^9 \) to \( 5 \times 10^{10} \) CFU.

In children who have already developed an allergy such as cow’s milk allergy (CMA), LGG supplementation may also be of benefit. One recent systematic review and meta-analysis of 10 studies on LGG (\( 1.4 \times 10^7–5 \times 10^9 \) CFU/day) reported that supplementation may aid recovery from GI symptoms, promote tolerance to the allergen and improve faecal blood. Evidence was rated as low-to-moderate quality, due to issues with blinding, concealment and unclear data; however, studies were RCTs. Tolerance acquisition following LGG supplementation in infants with IGE-mediated CMA may be due to its ability to influence gut microbiota structure, enabling colonisation of Oscillospira. The modulation of epigenetic mechanisms involved in the immune system and pathogenesis of CMA may also occur following LGG supplementation, resulting in increased tolerance to cow’s milk.

Immunomodulation by LGG has also been observed in adults with birch pollen allergy and oral allergy syndrome. This RCT of 38 patients received LGG (\( 2 \times 10^{10} \) CFU/day) for 5.5 months starting 2.5 months prior to allergy season resulting in increased allergen-specific immunoglobulin (Ig)A levels compared with baseline, effects that were not seen with placebo. This may be of benefit to symptoms, as IgA acts to prevent infections and maintain gut microbiota homeostasis, which if disrupted has been associated with an elevated risk of allergies in children. A second RCT on the effects of LGG supplementation (\( 3 \times 10^8 \) CFU/day) for 3 months on allergy in 141 marathon runners reported no effect on the immune marker IgE or several other allergic inflammatory markers, compared with placebo. Suboptimal dosages could be responsible for the lack of immunomodulatory effects in this trial, or the fact that the trial only looked at the inflammation-associated IgE and not the anti-inflammatory IgA. Although no symptom relief was observed in these trials, it is indicative of further immune effects in adults on IgA.

There is extensive clinical research on the efficacy and mechanisms behind the use of LGG to prevent allergic diseases and improve symptoms of CMA in children. Children at a high risk of developing allergic disease due to genetic predisposition, antibiotic use or C-section birth may benefit from at least \( 1 \times 10^9–5 \times 10^9 \) CFU/day for at least 3–6 months. Children with existing CMA may benefit from \( 1.4 \times 10^7–5 \times 10^9 \) CFU/day for at least 4 weeks and up to 3 years. Dosages of \( 2 \times 10^{10} \) CFU LGG may be of benefit to adults with birch pollen allergy for immunomodulation and the promotion of IgA. However, further studies are warranted to determine the significance of immunomodulation, as without effects on symptoms, supplementation may be pointless.

**Dermatitis and eczema**

Atopic dermatitis (ADE) is the most common chronic skin condition, affecting up to 20% of children and 3% of adults worldwide. Pathophysiology of ADEs is not fully understood; however, dysbiosis may be involved, as individuals with ADEs have lower diversity and levels of *Bifidobacterium* and *Actinobacteria*, and higher *Staphylococcus* than healthy subjects. Furthermore, studies indicate that like other atopic diseases, gut dysbiosis may contribute to ADE development through immunomodulation.

The effects of LGG supplementation on the immune system, as seen in patients with allergic disease, indicate a potential for its use in individuals with ADEs. An early systematic review and meta-analysis of five RCTs with 889 subjects concluded that LGG was ineffective for the primary prevention of eczema in children, when given both prenatally and postnatally. Dosages
ranged from $1 \times 10^9$ to $1.8 \times 10^9$ CFU per day, and the quality of data was good.

When looking at reduction of symptoms, recent RCTs not included in the above meta-analysis have shown differing results. Intrinsic microbiota at early infancy may affect outcomes, and infants with ADe who have higher levels of *Bifidobacterium dentium* have been shown to not respond to probiotic intervention, compared with those without disease. One RCT of 67 children with ADe concluded that LGG as the supplement ComProbi (350 mg) in combination with corticosteroid use was effective at decreasing symptoms of ADe after 8 weeks compared with placebo and corticosteroids (P = 0.014), based on Scoring of Atopic Dermatitis (SCORAD). However, it is difficult to determine that effects were due to LGG because corticosteroids were also being used. In a second RCT in 102 infants aged 3–12 months with ADe where corticosteroids were not used as the treatment, but were not precluded during the trial if individuals wanted to use them, no therapeutic effect of LGG based on SCORAD compared with placebo after 12 weeks was reported. Results from these two trials would suggest that corticosteroids and not LGG may account for the favourable outcomes.

As part of a multispecies therapy, LGG has shown more consistent results. When combined, LGG and *B. animalis* were shown in one systematic review and meta-analysis of 21 RCTs on various multispecies combinations to reduce the risk of ADe compared with placebo when administered in utero and during infancy. Furthermore, in a recent RCT of 290 children not included in the previous meta-analysis, the administration of LGG + *B. animalis* ($1 \times 10^9$ CFU/day) in late infancy for 6 months prevented the development of eczema, indicating that the use of LGG as part of a multispecies regime with *B. animalis* may be of benefit for the prevention of ADe and eczema.

The use of LGG for the primary prevention of ADe and eczema may be of benefit when used as part of a multispecies regime in combination with *B. animalis*, at a dose of $1 \times 10^9$ CFU/day, for at least 6 months. While there is yet no strong evidence for LGG alone, stratification of patients with ADe according to intrinsic microbiota may be of benefit for the improvement of symptoms following LGG use; however, more studies are required. The role of LGG in combination with corticosteroids also warrants more research.

### Wounds

The role of skin microbiota in wound healing is well documented, with both skin barrier function and the immune response reported to be microbially mediated. Topical application of probiotics for the treatment of burns has shown positive results; however, oral probiotic supplementation lacks research. It has been hypothesised that the gut microbiota communicates with the skin microbiota in a bi-directional manner through the gut–skin axis, evidenced by cutaneous manifestations following GI disorders. Oral LGG supplementation may have the potential to help treat certain skin diseases such as ADe and acne as documented above, therefore there may be potential for it to be of benefit to wound healing. The reduction of infections at incision sites in patients with cancer, detailed previously, indicates a benefit of LGG supplementation as part of a multispecies probiotic to aid postoperative healing. However, research on the effects in 20 burn victims found only a modest, non-significant improvement in the time taken to complete wound healing, and no improvements to other clinical outcomes.

There is no evidence for the use of LGG in combination with other probiotic strains for improvements to postoperative wounds. Research is lacking on monotherapy, and has found little effect on healing time in burn victims.

### Dental caries

The presence of *Streptococcus* and *Lactobacillus* spp. in the oral cavity has been associated with the presence and onset of dental decay. However, as previously discussed, LGG may have species-specific properties and produce an inhibitory microcin-like substance, which
Review

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has the ability to inhibit bacteria such as Streptococcus. In vitro studies have indicated that the consumption of an LGG probiotic may also be able to colonise the oral cavity and inhibit Streptococcus sobrinus. This may translate into a reduction in the risk of the development of caries. In one RCT, 594 children aged 1–6 years were given milk containing LGG (5–10 × 10⁵ CFU/ml) 5 days a week for 7 months, and showed a reduced risk of the development of dental caries (OR 0.56, 95% CI: 0.36–0.88, \( P = 0.01 \)), based upon Streptococcus levels from dental plaque and saliva, and the presence of dental caries.

Colonisation of the oral cavity may be affected by a lack of pili expression. There is only one trial on the use of LGG for the prevention of dental caries, as detailed above, and more studies are warranted given the mechanistic data. However, the trial that does exist was in many individuals over a relatively long period of time. It may therefore be of benefit to reduce the risk of dental caries in children and young adults. Dosages of at least 5–10 × 10⁵ CFU may be needed in children.

Vaccine adjuvant

The recent COVID-19 pandemic and ability of SARS-CoV-2 to mutate has highlighted a need to improve immune response following vaccination. Orally ingested LGG may modulate the immune system in response to bacteria and viruses involved in the development of diseases. Research in mice given oral Lactobacillus has reported enhanced innate immune response following influenza virus challenge, with increased influenza-specific IgG antibodies and greater protection. RCTs have indicated that LGG may be a useful adjuvant for the immune response following influenza vaccine. One RCT in 42 healthy adults reported increased protection to the H3N2 influenza strain whilst supplementing LGG (1 × 10⁹ CFU) and inulin for 28 days following vaccination. However, in the same study, no differences in seroprotection to the H1N1 or B influenza strains were observed.

Individuals with type 1 diabetes (T1D) are at increased risk of infections, and influenza vaccine is recommended; however, whether influenza vaccines are truly successful in this cohort is still being debated. Adjuvants to increase the immunogenicity of the influenza vaccine may be important, and use of LGG (1 × 10⁹ CFU) 3 months pre- and post-influenza vaccination in 64 paediatric patients with T1D reduced the inflammatory immune response associated with T1D, decreasing IL-17, IFN-\( \gamma \), IL-6 and TNF-\( \alpha \), without affecting the seroprotective antibodies, which are needed for effective vaccination. However, although antibody-mediated immunity remained unaffected in this trial, the mediation of the inflammatory response may be important for individuals who suffer from autoimmune diseases such as T1D.

Studies on different types of vaccinations and studies on LGG as an adjuvant to the polio, rotavirus, Hib, diphtheria and tetanus vaccinations have been completed with varying success. One RCT of 66 healthy males reported that the use of LGG (1 × 10⁹ CFU), as an adjuvant to the polio vaccine, nearly doubled the increase of polio-specific IgG antibodies and significantly increased IgA antibodies, compared with placebo. A second RCT of 98 pregnant women given LGG (5 × 10⁹ CFU) resulted in more frequent occurrence of higher Hib antibody concentrations following vaccination with Hib, diphtheria and tetanus in the offspring; however, IgG remained unaffected. In contrast, LGG supplementation (1 × 10⁹ CFU) marginally but not significantly improved rotavirus antibodies following vaccination in 620 infants. This may correspond to the findings above regarding LGG competitively inhibiting and acting as an antimicrobial against rotavirus, which could prevent the body from becoming infected and building an enhanced immune response when the body is faced with the live rotavirus as part of a vaccine.

The use of LGG supplementation (at least 1 × 10⁹ CFU) as part of a vaccine adjuvant has been shown to be of benefit to the success of the response of biomarkers to vaccines, but only following influenza H3N2, polio and Hib. Further research needs to be performed with other vaccinations to determine effects.
Safety

Probiotics belonging to the genus *Lactobacillus* and *Bifidobacterium* are generally regarded as safe (GRAS) by the United States Food and Drugs Administration (FDA). However, some studies on *Lactobacillus* have reported bacteraemia in specific populations, primarily amongst immunocompromised paediatric patients. In adults, incidences of bacteraemia-associated endocarditis, primarily in those with a structural heart defect, have also been reported. A recent systematic review has indicated that LGG may increase the risk of complications in patients who are immunocompromised, who have critical illnesses, structural heart disease or who have a central venous catheter. In pregnancy and lactation, a recent meta-analysis and systematic review concluded that probiotics are safe for use during pregnancy and lactation. Data from the trials included in this review showed that adverse events in pregnancy and lactation following LGG supplementation were minor, and one systematic review and meta-analysis has concluded that probiotic use is safe during pregnancy and lactation; however, it would still be recommended to consult with a doctor prior to commencement.

Drug–nutrient interactions are very few, with minor warnings whilst on anti-diabetes drugs due to potential hypoglycaemia and moderate interactions whilst taking antibiotic drugs, as LGG efficacy may be reduced.

Conclusion

The unique morphological features of LGG may ensure that it has some use as an oral supplement in the reduction of risk of developing ADHD and GDM, in the prevention of allergies and dental caries, for improving immune reactions following vaccines, and for the management of diarrhoea associated with cancer treatments and antibiotic use. Three ways in which it may do this are through immunomodulation, cell growth and proliferation, and as an antimicrobial, aiding it to promote eubiosis. This results in LGG acting to prevent disease development, help manage symptoms and improve underlying pathology. The presence of pili on the exterior aid its colonisation of the GI tract, and its lack of efficacy in disease areas such as UTIs may be due to a lack of expression of these features in certain areas of the body. Effects may be systemic if there is a pathway through which LGG or its products can travel, like the gut–brain axis. However, effects may also be localised and specific, if a transmission pathway does not exist, as seen with its success only in specific cancer types, and diarrhoea treatment in colorectal cancer but not HIV.

There are, however, limitations of this study, and the inability to address genetic variation amongst LGG is apparent. Genetic variants have been found within the LGG species resulting in variations that do not have the *spaCBA* gene. These variants may lack the ability to express the pili-like projections responsible for many of the physiological effects attributed to LGG. It is therefore difficult to exclude the possibility that positive or negative results were not attributable to within-strain differences. Until the research is performed, it is difficult for practitioners to determine which commercial products may have genetic variations. It may be that quality assurance legislation needs to be put in place; however, this has yet to be enacted. A second limitation is that this study could not account for individual intrinsic gut microbiota populations, which are highly personalised. Therefore, although patients or disease areas may have been identified to benefit from LGG supplementation, differences between intrinsic gut microbiota may affect efficacy. Amongst the studies, issues with small sample sizes, contradictory results and the fact that the large majority of the research involved the use of multispecies supplements, and the use of other treatments and therapies amongst some of the research, means that conclusions need to be interpreted with caution.
## Appendix

### Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Intervention period, treatment dose</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Armuzzi et al.⁴⁷ Italy RCT</td>
<td>To determine the effect of perioperative use of multispecies placebo + oligosaccharide in patients with colorectal cancer</td>
<td>LGG + Lactobacillus acidophilus + Lactobacillus casei + Bifidobacterium (all 1 × 10⁸ CFU/day) + fructo-oligosaccharide (6 g) versus placebo, 12 weeks</td>
<td>91 patients undergoing surgery for colorectal cancer</td>
<td>Infection occurring within 30 days of surgery</td>
<td>Perioperative administration of synbiotics reduced the occurrence of postoperative infections in patients with colorectal cancer</td>
<td>Not stated</td>
</tr>
<tr>
<td>Flesch et al.³ Brazil RCT</td>
<td>To determine the effect of daily intake of multispecies probiotic + fructo-oligosaccharides</td>
<td>LGG + B. lactis Bbt12 + inulin (SYN1 brand), 12 g sachet per day, 12 weeks</td>
<td>37 patients with colon cancer and 43 polypoid patients</td>
<td>Not stated</td>
<td>Probiotics may alter several colorectal cancer biomarkers Probiotic changed Bifidobacterium, Lactobacillus and Clostridium perfringens Decreased level of DNA damage in polyp patients Increased IL-2 secretion prevented in polyp patients but not cancer Increased IFN-γ in patients with cancer but not polyp group</td>
<td>Limited biopsies</td>
</tr>
<tr>
<td>Lages et al.⁴⁸ Brazil RCT</td>
<td>To determine whether multispecies probiotic + prebiotic can reduce the risk of colon cancer</td>
<td>LGG + B. lactis (1 × 10⁹ CFU/day) + 10 g inulin versus placebo, 12 weeks compared with baseline</td>
<td>34 patients with colon cancer who had undergone curative resection and 40 polypoid patients</td>
<td>Phagocytic and respiratory burst activity of neutrophils and monocytes, lytic activity of NKCs, transforming growth factor, prostaglandin E2 and inflammatory markers</td>
<td>Supplementation with multispecies probiotic had modest effects on the immune system of the two study groups IL-2 significantly increased in the cancer group (P &lt; 0.05) between 0 weeks or 6 weeks and 12 weeks IFN-γ increased at 12 weeks (P &lt; 0.05) No other immune factors affected</td>
<td>Limited biopsies</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; GI, gastrointestinal; IFN-γ, interferon-gamma; IL, interleukin; LGG, Lactobacillus rhamnosus GG; NKCs, natural killer cells; RCT, randomised-controlled trial; RR, relative risk.
### Irritable bowel syndrome

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<tr>
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<tbody>
<tr>
<td>Francavilla et al.⁴</td>
<td>To determine whether LGG relieves symptoms in children with recurrent abdominal pain</td>
<td>16 weeks (8 weeks treatment, 8 weeks follow-up) 6 × 10⁹ CFU/day</td>
<td>141 children with IBS or functional pain</td>
<td>Change in abdominal pain according to VAS score</td>
<td>LGG but not placebo reduced frequency and severity of abdominal pain from baseline. Effects may be due to improvement of gut barrier</td>
<td>Effect may not be unique to LGG. Did not assess gut microbiota at baseline or end. Cannot exclude possibility that effect is short-lived</td>
</tr>
<tr>
<td>Horváth et al.¹⁸</td>
<td>To assess the effect of LGG for treating abdominal pain-related functional GI disorders in children compared with no treatment or placebo</td>
<td>3 RCTs, 290 children with abdominal pain-related functional GI disorders</td>
<td>Study 1: change in abdominal pain score Study 2: VAS Study 3: Faces pain scale</td>
<td>Beneficial effect of LGG in IBS Intensity and frequency of pain significantly reduced</td>
<td>Did not perform a statistical test for publication bias</td>
<td></td>
</tr>
<tr>
<td>Lyra et al.¹⁴</td>
<td>To determine if a multispecies probiotic can affect IBS-associated microbiota alterations</td>
<td>6 months LGG + Lactobacillus rhamnosus Lc705, Propionibacterium freudenreichii spp. shermanii JS and Bifidobacterium Bl99 8−9 × 10⁹ CFU/day</td>
<td>42 patients with IBS</td>
<td>Changes in faecal microbial composition</td>
<td>Multispecies probiotic altered IBS-associated microbiota quantities of the bacterial 16S rDNA phylotypes, to those reflective of IBS-free subjects, particularly Clostridium thermosuccinogenes</td>
<td>Not stated</td>
</tr>
<tr>
<td>Pedersen et al.⁶⁶</td>
<td>Investigate the effects of a low-FODMAP diet versus LGG in IBS</td>
<td>6 weeks, 6 × 10⁹ CFU/day (Dicoflor 60 capsules)</td>
<td>123 males and females with IBS</td>
<td>Disease severity of IBS using IBS-SSS questionnaire</td>
<td>Both treatments efficacious for IBS, especially in the IBS-D and IBS-A subtypes</td>
<td>Lack of blinding Not placebo controlled Diet adherence not evaluated</td>
</tr>
<tr>
<td>Wegh et al.²⁷</td>
<td>Investigate the effects of probiotics on FAPD and functional constipation in children</td>
<td>17 studies with 1321 children (3 on LGG)</td>
<td>LGG reduces frequency and severity of abdominal pain, but only in children with IBS</td>
<td></td>
<td></td>
<td>Majority of studies have unclear or high risk of bias Many studies did not compare the results from baseline, only between groups High heterogeneity between groups Only studies in English included Crossover studies included Studies only had a 2-week washout period</td>
</tr>
<tr>
<td>Yoon et al.²⁷</td>
<td>Investigate the efficacy of a multispecies probiotic on IBS symptoms and gut microbiota alterations</td>
<td>4 weeks multispecies, 5 × 10⁹ CFU/day LGG + Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus and Streptococcus thermophilus</td>
<td>49 patients with IBS</td>
<td>Proportion of patients who experience IBS symptom relief based on answers to two questions</td>
<td>Multispecies probiotic supplementation is effective at relieving symptoms of abdominal pain, bloating and discomfort in individuals with IBS, and caused a change to the gut microbiota</td>
<td>Faecal analysis not in whole study population Faecal microbiota analysis only reflects bacterial composition in the intestinal lumen Validated measurement of symptom improvement was not used Did not look at gender or IBS subtypes</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; FAPD, functional abdominal pain disorders; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-A, IBS-mixed subtype; IBS-D, IBS-diarrhoeal subtype; IBS-SSS, IBS-Severity Scoring System; LGG, Lactobacillus rhamnosus GG; RCT, randomised-controlled trial; VAS, Visual Analogue Scale.
### Diarrhoea

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Agamennone et al.</td>
<td>To produce a guide on the use of probiotics to prevent AAD</td>
<td></td>
<td>32 RCTs</td>
<td></td>
<td>Results indicate that seven single or multispecies favouring the treatment group, with LGG being the most effective (RR = 0.30 versus placebo, 95% CI: 0.16–0.5)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Fang et al.</td>
<td>To assess whether there is a dose-dependent effect of LGG on the reduction of faecal rotavirus shedding in children</td>
<td>0 CFU/day in control 2 × 10⁹ CFU/day low dose 6 × 10⁶ CFU/day high dose</td>
<td>23 children with acute rotaviral gastroenteritis</td>
<td>Not stated</td>
<td>Low-dose group had no change in faecal rotavirus concentrations (361 × 10⁵ particles/ml versus 73.5 × 10⁵ particles/ml, P = 0.895); however, the high-dose group did (64.2 × 10⁵ particles/ml versus 9.0 × 10⁵ particles/ml, P = 0.012)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Korpeia et al.</td>
<td>To determine the effect of long-term LGG consumption on pre-school children’s antibiotic use. Also assessed its effect on gut microbiota</td>
<td>400 ml milk containing 10⁵ CFU/ml LGG for 7 months</td>
<td>231 school-aged children</td>
<td>First antibiotic purchase</td>
<td>Long-term LGG may prevent specific bacterial infections for up to 3 years, and may prevent some of the gut microbiota changes associated with antibiotic use. Increased abundance of the Lactobacillus spp. (P &lt; 0.001)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Li et al.</td>
<td>Evaluate the efficacy of LGG in children with acute diarrhoea</td>
<td>19 RCTs</td>
<td></td>
<td>Development of persistent diarrhoea, including duration</td>
<td>High-dose LGG reduced duration and frequency of diarrhoea episodes. Results pronounced in those who were treated early and who presented with rotavirus-positive diarrhoea. Reduced duration (MD = −31.05 hours, 95% CI: 50.31, −11.80) and frequency of episodes (MD = −10.8, 95% CI: −1.87, −0.28)</td>
<td>Limitations amongst the studies included limited pathogen identification, small sample sizes, varying dosages and limited blinding</td>
</tr>
<tr>
<td>Schnadower et al.</td>
<td>Determine the effectiveness of a 5-day course of LGG compared with placebo in children with acute gastroenteritis</td>
<td>5 days, 1 × 10¹⁵ CFU twice daily versus placebo</td>
<td>943 children aged 3 months to 4 years with acute gastroenteritis</td>
<td>Presence of moderate-to-severe gastroenteritis</td>
<td>Administration of LGG to preschool children with acute gastroenteritis did not result in a smaller number of moderate-to-severe gastroenteritis cases, and did not show benefit to duration or frequency of vomiting or diarrhoea compared with children receiving placebo.</td>
<td>Possible inaccurate recall by participants. Potential for LGG preparation to be inadequately stored</td>
</tr>
<tr>
<td>Szajewska et al.</td>
<td>To provide recommendations on the use of probiotics and prebiotics for the prevention of AAD in children</td>
<td></td>
<td>20 RCTs</td>
<td>Diarrhoea/AAD and Clostridium difficile-associated diarrhoea</td>
<td>Recommended using LGG or Saccharomyces boulardii for preventing AAD. For C. difficile-associated diarrhoea then LGG not recommended. AAD risk reduction (RR = 0.48, 95% CI: 0.26–0.89)</td>
<td>The authors question the validity of pooling different strains of probiotic, when they all have differing effects</td>
</tr>
<tr>
<td>Szajewska &amp; Kołodziej</td>
<td>To determine the efficacy of LGG to prevent AAD in children and adults</td>
<td></td>
<td>12 RCTs, 1499 participants</td>
<td>Incidence of diarrhoea or AAD</td>
<td>Treatment with LGG compared with placebo or no additional treatment reduced the risk of AAD from 22.4% to 12.3% (RR = 0.49, 95% CI: 0.29–0.83, NNT = 9)</td>
<td>Definition of AAD varied amongst studies. Unclear risk of bias</td>
</tr>
</tbody>
</table>

AAD, antibiotic-associated diarrhoea; CFU, colony-forming units; CI, confidence interval; LGG, Lactobacillus rhamnosus GG; MD, mean difference; NNT, number needed to treat; RCT, randomised-controlled trial; RR, relative risk.
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Inflammatory bowel disease

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</thead>
<tbody>
<tr>
<td>Bousvaros et al.²¹ USA RCT</td>
<td>To determine if addition of LGG to standard therapy prolonged remission in children with Crohn’s disease</td>
<td>2-year follow-up, LGG 10⁷ CFU/day + 295 mg inulin versus placebo</td>
<td>75 children aged 5-21 years</td>
<td>Time to clinical relapse</td>
<td>Median time to relapse 9.8 months in LGG versus 11.0 months in placebo group (P = 0.24) LGG did not prolong remission in children with Crohn’s disease Concomitant therapies could be masking effects of LGG</td>
<td></td>
</tr>
<tr>
<td>Jonkers et al.⁷⁹ Netherlands Systematic review and meta-analysis</td>
<td>Assess the use of probiotics in IBD management</td>
<td>41 RCTs, two in LGG</td>
<td>No difference in LGG supplementation and placebo for endoscopic recurrences in inactive Crohn’s disease, even though there was an OR of 0.93 (95% CI 0.63, 1.38) High drop-out rates amongst studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorea Baroja et al.⁸² Canada Open-labelled study</td>
<td>Assess whether a combination of LGG GR-1 strain and Lactobacillus rhamnosus in a yoghurt supplement was able to promote an anti-inflammatory state in individuals with Crohn’s disease</td>
<td>125 g probiotic yoghurt per day for 30 days LGG dosage 2 × 10² CFU/ml and L. rhamnosus 1 × 10³ CFU/ml</td>
<td>20 participants with Crohn’s disease and ulcerative colitis, 20 healthy controls</td>
<td>Changes in the prevalence of inflammatory markers Treg cells (CD4⁹ CD25⁹), TNF-α and IL-12</td>
<td>Amongst patients with IBD, increased CD4⁹ CD25⁹⁹ T-cells (P = 0.007) This correlated with a decrease in the percentage of TNF-α and IL-12 Probiotic yoghurt intake was associated with an anti-inflammatory effect</td>
<td></td>
</tr>
<tr>
<td>Shen et al.⁸⁰ China Meta-analysis</td>
<td>Assess the effect and adverse events of Lactobacillus strains compared with placebo as maintenance therapy in Crohn’s disease</td>
<td>6 RCTs, 4 trials in LGG 359 individuals</td>
<td>Clinical relapse rates</td>
<td>LGG may increase the relapse rate of those with Crohn’s disease Significant benefit of placebo (RR = 1.68, 95% CI 1.07–2.64)</td>
<td>Not stated</td>
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</table>

Limitations

- High drop-out rates amongst studies
- Different measures of relapse rates amongst the studies

Body weight

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Callaway et al.⁹¹ RCT Australia</td>
<td>To determine whether multispecies probiotic in overweight and obese women prevents GDM</td>
<td>Probiotic LGG + Bifidobacterium animalis 1 × 10⁹ CFU/day versus placebo</td>
<td>411 pregnant overweight and obese women</td>
<td>Frequency of GDM at 28 weeks gestation Secondary outcomes: gestational weight gain, preeclampsia, hypertension, Caesarean delivery, and gestation age of delivery</td>
<td>Probiotics did not prevent GDM (18.4% probiotic versus 12.3% placebo, P = 0.10), but did prevent excessive weight gain during gestation in overweight and obese pregnant women (32.5% probiotic versus 46% placebo, P = 0.01)</td>
<td>Oral glucose tolerance test not completed at start of trial Changes to trial design meant some women only taking probiotics for 1-4 weeks</td>
</tr>
<tr>
<td>Kekkonen et al.⁹² RCT sub-study</td>
<td>To determine the effect of LGG supplementation on serum lipid profiles and inflammatory markers</td>
<td>250 ml milk-based fruit drink with LGG 6.2 × 10⁵ CFU/ml for 3 weeks</td>
<td>26 healthy adults</td>
<td>Not stated</td>
<td>LGG supplementation may lead to a change in serum global lipid profiles Decreased LysoGPCho (P ≤ 0.05), sphingomyelins (P ≤ 0.005) and glycerophosphatidylcholines (P ≤ 0.05)</td>
<td>When allowing for multiple hypothesis testing, no changes in global lipidomic profiles</td>
</tr>
<tr>
<td>Oksene-Gafa et al.⁸⁰ RCT New Zealand</td>
<td>To determine a culturally tailored dietary intervention and/or daily probiotic in obese pregnant women reduces gestational weight gain and birth weight</td>
<td>Dietary intervention versus routine dietary advice + probiotic containing LGG and Bifidobacterium lactis BBD 6.5 × 10⁹ CFU/day until birth</td>
<td>230 obese pregnant women and their babies</td>
<td>Proportion of women with excessive gestational weight gain Birth weight</td>
<td>Neither treatment had a significant effect Total maternal weight gain was lower with dietary intervention than probiotic and routine dietary advice (87 kg versus 11.4 kg, adjusted MD −176, 95% CI: 3.55−0.03)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; IBD, inflammatory bowel disease; IL, interleukin; LGG, Lactobacillus rhamnosus GG; OR, odds ratio; RCT, randomised-controlled trial; RR, relative risk; TNF-α, tumour necrosis factor-alpha.
**Liver disease**

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<thead>
<tr>
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<tbody>
<tr>
<td>Kwak et al.</td>
<td>To determine the efficacy of probiotics to improve SIBO and gut permeability in liver disease</td>
<td>Multispecies containing 5 × 10⁹ CFU <em>Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus</em> and <em>Streptococcus thermophilus</em> versus placebo, once daily for 4 weeks</td>
<td>53 patients with chronic liver disease</td>
<td>Changes in the composition of faecal bacteria, SIBO, intestinal permeability and clinical symptoms</td>
<td>LGG increased in faeces of probiotic group (P ≤ 0.001) SIBO significantly disappeared in probiotic group compared with placebo (P ≤ 0.05) Intestinal permeability improved but not significantly Liver chemistry remained unaffected Short-term probiotics effective in alleviating SIBO but not liver function in patients with chronic liver disease</td>
<td>Hydrogen breath test not jejunal aspiration used to test for SIBO Study participants had only mild disease as administration of probiotics in immunocompromised individuals is not recommended</td>
</tr>
<tr>
<td>Vajro et al.</td>
<td>To evaluate the effects of short-term probiotic treatment in children with NAFLD</td>
<td>LGG 1.2 × 10⁹ CFU/day for 8 weeks</td>
<td>20 children with NAFLD</td>
<td>Not stated</td>
<td>Compared with placebo, LGG was associated with a decrease in ALT (P = 0.03) and in anti-peptidoglycan-polysaccharide antibodies (P = 0.03) LGG should be considered as a therapy for children with NAFLD who do not comply with lifestyle interventions</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CFU, colony-forming units; LGG, *Lactobacillus rhamnosus* GG; NAFLD, non-alcoholic fatty liver disease; RCT, randomised-controlled trial; SIBO, small intestinal bacterial overgrowth.

**Insulin resistance and type 2 diabetes**

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Assemi et al.</td>
<td>To determine the effect of multispecies probiotic on metabolic profiles</td>
<td><em>Lactobacillus acidophilus</em> (2 × 10⁸ CFU), <em>Lactobacillus casei</em> (7 × 10⁹ CFU), LGG (5 × 10⁸ CFU), <em>Lactobacillus bulgaricus</em> (2 × 10⁹ CFU), <em>Bifidobacterium breve</em> (2 × 10⁹ CFU), <em>Bifidobacterium longum</em> (7 × 10⁹ CFU), <em>Streptococcus thermophilus</em> (1.5 × 10⁹ CFU) versus placebo, 8 weeks</td>
<td>54 diabetic patients</td>
<td>Anthropometrics Plasma glucose HbA1c levels HOMA-IR blood lipid concentrations Antioxidants</td>
<td>Multispecies probiotic for 8 weeks in patients with diabetes prevented a rise in fasting plasma glucose, and decreased serum hs-CRP and increased GSH Measures of IR were increased in both groups, but less so in the probiotic group (P = 0.03)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Laitinen et al.</td>
<td>To determine whether supplementation of multispecies probiotic with dietary counselling affects glucose metabolism in normoglycaemic pregnant women</td>
<td>LGG + <em>Bifidobacterium lactis</em> + dietary advice versus placebo during pregnancy and 12 months post-partum Dosage not stated</td>
<td>256 normoglycaemic pregnant women</td>
<td>Glucose metabolism through plasma glucose concentration and HbA1c, serum insulin and HOMA and QUICKI</td>
<td>In normoglycaemic pregnant women, diet + probiotics may improve blood glucose control Blood glucose at lowest in diet + probiotic group during pregnancy and 12 months post-partum (P ≤ 0.025 for both) Better glucose tolerance in diet + probiotic group through HOMA-IR (P = 0.028) insulin concentration (P = 0.032) and QUICKI (P = 0.028) Reduced risk of elevated glucose concentration compared with placebo (OR 0.31, 95% CI: 0.22, 0.78, P = 0.0028)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Sanborn et al.</td>
<td>To determine whether probiotic supplementation improves glycaemic control in healthy individuals</td>
<td>LGG 1 × 10⁹ CFU versus placebo, 90 days</td>
<td>200 healthy middle-aged and older adults</td>
<td>HbA1c</td>
<td>LGG may help maintain glycaemic control in healthy adults HbA1c increased in placebo but maintained in the LGG group between-group difference P = 0.0059</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; GSH, glutathione; HbA1c, glycated haemoglobin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; IR, insulin resistance; LGG, *Lactobacillus rhamnosus* GG; OR, odds ratio; QUICKI, Quantitative Insulin-Sensitivity Check Index; RCT, randomised-controlled trial.
## Cystic fibrosis

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Bruzese et al.</td>
<td>To determine the gut microbiota composition of children with CF, and whether correlations between microbial balance and inflammation exist. Then to determine whether LGG restores intestinal flora and decreases inflammation</td>
<td>6 × 10⁹ CFU versus placebo daily for 1 month</td>
<td>22 children with CF</td>
<td>Intestinal inflammation</td>
<td>Bacterial composition</td>
<td>CF restored gut microbiota reducing intestinal inflammation and pulmonary exacerbations. LGG reduced faecal CLP (184 ± 146 mg/g versus 52 ± 46 mg/g; ( P &lt; 0.01 )). Correlation between reduced microbial richness and intestinal inflammation (( r = 0.53; \ P = 0.018 ))</td>
</tr>
<tr>
<td>Bruzese et al.</td>
<td>To investigate the effects of LGG on clinical outcomes of children with CF</td>
<td>LGG 6 × 10⁹ CFU/day versus placebo, 12 months</td>
<td>95 children with CF</td>
<td>Proportion of subjects with at least one pulmonary exacerbation over the 12-month study period</td>
<td>LGG had no effect on respiratory and nutritional outcomes in children with CF. Odds of experiencing at least one exacerbation were not significantly different from placebo (OR 0.83, 95% CI: 0.38–1.82, ( P = 0.643 )). The odds of hospitalisations also remained unaffected (OR 167, 95% CI: 0.75–3.72, ( P = 0.211 ))</td>
<td>Not stated</td>
</tr>
<tr>
<td>Bruzese et al.</td>
<td>To assess the incidence of intestinal inflammation in children with CF, and whether probiotics decrease it</td>
<td>LGG 5 × 10⁹ CFU/day</td>
<td>75 children (30 with CF, 30 with IBD and 15 healthy controls)</td>
<td>Intestinal inflammation</td>
<td>is a feature of CF as indicated by increased CLP (versus control, ( P &lt; 0.01 )) similar to levels of children with IBD (( P &gt; 0.05 )). Intestinal microflora play a major role in this</td>
<td>LGG reduced inflammation (210 ± 42 to 140 ± 43 mg/g, ( P = 0.01 ))</td>
</tr>
<tr>
<td>Bruzese et al.</td>
<td>To determine the effect of LGG on pulmonary exacerbations in children with CF</td>
<td>LGG 6 × 10⁹ CFU/day for 6 months and then shifted to dissolved oral rehydration solution for 6 months. Or dissolved oral rehydration solution for 6 months and then LGG for 6 months</td>
<td>43 children with CF</td>
<td>Incidence and severity of pulmonary exacerbations</td>
<td>Number and duration of hospital admissions Route of antibiotic administration (indication of severity of episode) FEV₁ Body weight Serum immunoglobulin concentrations</td>
<td>LGG reduced pulmonary exacerbations and hospital admissions in children with CF. Pulmonary exacerbations reduced (group A, median difference 1, CI 95%; 0.1–2, ( P = 0.035 ); Group B, median difference 1, 95% CI: 0–2, ( P = 0.02 )). Rate of hospital admissions (LGG = 16, ORS = 32). Significant differences only in period one (MD 1, 95% CI: 0.1–1, ( P = 0.01 )). Mean duration of hospital stay did not differ between the two groups</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; CFU, colony-forming units; CI, confidence interval; CLP, calprotectin; FEV₁, forced expiratory volume; IBD, inflammatory bowel disease; LGG, Lactobacillus rhamnosus GG; MD, mean difference; OR, odds ratio; RCT, randomised-controlled trial.
# Respiratory Tract Infections

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Liu et al.23</td>
<td>To review the effectiveness of LGG for the prevention of respiratory infections in children</td>
<td>4 RCTs, 1805 children</td>
<td></td>
<td>Incidence of respiratory infections</td>
<td>LGG may reduce the incidence of otitis media, URTIs and antibiotic use in children. LGG was associated with reduced otitis media (RR = 0.76, 95% CI: 0.64−0.91, NNT = 17), reduced risk of URTIs (RR = 0.62, 95% CI: 0.50−0.78, NNT = 4) and antibiotic use (RR = 0.80, 95% CI: 0.71−0.91). Risk of overall respiratory infections was only reduced in those older than 1 year (RR = 0.73, 95% CI: 0.57−0.92, NNT = 8). No difference in the incidence of lower respiratory infections.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Hojsak et al.25</td>
<td>To determine the role of LGG in preventing nosocomial GI infections and RTIs in children</td>
<td>LGG 1 × 10⁹ CFU/day in 100 ml of a fermented milk product versus placebo, Duration not stated</td>
<td>742 hospitalised children</td>
<td>GI tract infections</td>
<td>LGG can decrease risk for nosocomial GI infections and RTIs in paediatric facilities. Reduced risk of RTIs compared with placebo (RR = 0.38, 95% CI: 0.18−0.85, NNT = 30). No difference in hospitalisation duration.</td>
<td>Infants prone to severe nosocomial infections were excluded. The study period in most cases was short. Cause of nosocomial infection was often unknown.</td>
</tr>
<tr>
<td>Tapiovaara et al.85</td>
<td>To determine whether beneficial effects of LGG in RTIs are due to a reduced viral load</td>
<td>LGG 1 × 10⁹ CFU/day versus placebo, 6 weeks</td>
<td>59 adults given human rhinovirus</td>
<td>Viral load</td>
<td>The use of LGG did not affect viral load in individuals with human rhinovirus. Viral load LGG versus placebo (P = 0.57).</td>
<td>Samples collected 5 days after given human rhinovirus. Validated symptom survey not used.</td>
</tr>
<tr>
<td>Kumpu et al.86</td>
<td>To determine whether inactivated LGG would demonstrate similar effects to live LGG in humans with induced rhinovirus infection</td>
<td>LGG 1 × 10⁹ CFU in 100 ml fruit juice, 6 weeks</td>
<td>60 individuals induced with the human rhinovirus</td>
<td>Occurrence, duration and severity of cold symptoms</td>
<td>Live LGG may be more effective in reducing rhinovirus infection than the inactivated form, but differences were not significant. Occurrence and severity of cold symptoms was lowest in the LGG live group, but this was not statistically significant due to the pilot-scale of study (P = 0.45).</td>
<td>Not stated</td>
</tr>
<tr>
<td>Laursen &amp; Hojsak122</td>
<td>To evaluate strain-specific effects of probiotics on RTIs in children at day care</td>
<td>15 RCTs with 5121 children in daycare</td>
<td>Number of children with RTIs</td>
<td>Of the probiotics analysed, LGG significantly reduced the duration of RTIs (MD = −0.78 days, 95% CI: −1.46, −0.09), but no effect on incidence, antibiotic use or days missed from daycare.</td>
<td>Studies included differed in methodological quality. Only included studies in English.</td>
<td>Data on infant illness recorded using questionnaires.</td>
</tr>
<tr>
<td>Laursen et al.25</td>
<td>To determine the effects of multispecies probiotic on absence from childcare due to respiratory and GI infections in healthy infants</td>
<td>LGG + Bifidobacterium animalis 1 × 10⁹ CFU, 6 months</td>
<td>290 infants who attend childcare</td>
<td>Number of days absent from childcare because of respiratory or GI infections</td>
<td>A multispecies probiotic for 6 months did not affect the number of days absent from childcare in healthy infants (P = 0.19).</td>
<td></td>
</tr>
</tbody>
</table>
**CFU**, colony-forming units; CI, confidence interval; GI, gastrointestinal; LGG, *Lactobacillus rhamnosus* GG; MD, mean difference; NNT, number needed to treat; RCT, randomised-controlled trial; RR, relative risk; RTI, respiratory tract infection; URTI, upper respiratory tract infection.

### Otitis media

<table>
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<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Lehtoranta et al.</td>
<td>To determine the prevalence and persistence of HBoV, and whether multispecies probiotics reduce occurrence</td>
<td>LGG + <em>Lactobacillus rhamnosus</em> Lc705 + <em>Bifidobacterium breve</em> 99 and <em>Propionibacterium freudenreichii</em> JS (dosage not stated) versus placebo, 6 months</td>
<td>269 otitis-prone children</td>
<td>Not stated</td>
<td>Probiotic treatment may reduce the presence of HBoV in children</td>
<td>Not stated</td>
</tr>
<tr>
<td>Tapiovaara et al.</td>
<td>To determine the effect of 3-week oral administration of LGG on MEE in children with otitis media</td>
<td>8−9 × 10⁹ CFU/day versus placebo, 3 weeks</td>
<td>40 children undergoing tympanostomy</td>
<td>LGG findings in MEE</td>
<td>LGG was detected in the middle ear of children with otitis media, but did not affect the occurrence of bacteria or viruses</td>
<td>Small study size; PCR-assay used may not be optimised to detect bacteria in MEE</td>
</tr>
<tr>
<td>Hatakka et al.</td>
<td>To determine the effect of multispecies probiotic</td>
<td>LGG + <em>L. rhamnosus</em> Lc705, <em>B. breve</em> 99 and <em>P. freudenreichii</em> JS 8−9 × 10⁹ CFU/day versus placebo, 24 weeks</td>
<td>309 otitis-prone children</td>
<td>Occurrence and duration of acute otitis media episodes</td>
<td>Probiotic treatment did not reduce the occurrence (probiotic versus placebo, 72% versus 65%, OR 1.48, 95% CI: 0.87−2.52, P = n.s.), reoccurrence (18% versus 17%, OR 1.04, 95% CI: 0.55−1.96, P = n.s.) or duration (5.6 versus 6.0 days, P = n.s.)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
**Anxiety and depression**

<table>
<thead>
<tr>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Dawe et al. 143</td>
<td>A secondary analysis to determine whether probiotics would improve maternal mental health</td>
<td>LGG + Bifidobacterium lactis 6.5 × 10^9 CFU/day versus placebo Duration not stated</td>
<td>230 women at 36 weeks of pregnancy</td>
<td>Depression Anxiety Functional health and wellbeing</td>
<td>Probiotics did not improve the mental health of pregnant women at 36 weeks gestation No difference between depression scores (P = 0.05) Anxiety and physical wellbeing worsened over time, and mental wellbeing did not differ at 36 weeks</td>
<td>Probiotic strain used may not be optimal Dosage may not be optimal Adherence to treatment was via self-reporting not capsule count Small sample size</td>
</tr>
<tr>
<td>Mohammadi et al. 135</td>
<td>To determine the effects of multispecies probiotic and probiotic yoghurt on mental health and hypothalamic-pituitary axis</td>
<td>Yoghurt contained 1 × 10^7 CFU Lactobacillus acidophilus + 8 lactis Multispecies probiotic contained Lactobacillus casei 3 × 10^7 CFU, L acidophilus 3 × 10^7 CFU, LGG 7 × 10^8 CFU, Lactobacillus bulgaricus 5 × 10^9 CFU, Bifidobacterium breve 2 × 10^9 CFU, Bifidobacterium longum 1 × 10^9 CFU, Streptococcus thermophilus 3 × 10^9 CFU</td>
<td>70 petrochemical workers</td>
<td>GHQ DASS scores</td>
<td>Improvements within probiotic yoghurt group in GHQ (8.0 ± 15 versus 13.5 ± 19, P = 0.007) and DASS (23.3 ± 37 versus 13.0 ± 37, P = 0.02) Improvements within the probiotic capsule group in GHQ (16.9 ± 18 versus 9.8 ± 19, P = 0.001) and DASS (18.9 ± 3.2 versus 9.4 ± 4.0, P = 0.006) No improvements in conventional yoghurt group for GHQ (P = 0.05) or DASS (P = 0.08)</td>
<td>Short supplementation period Did not assess short-chain fatty acid production</td>
</tr>
<tr>
<td>Moludi et al. 135</td>
<td>To determine the effects of probiotics on symptoms of depression, measures of QoL, oxidative stress and inflammation in individuals who had recently had a MI</td>
<td>Secondary analysis LGG 16 × 10^9 CFU/day versus placebo, 12 weeks</td>
<td>44 adults with recent MI and PCI</td>
<td>Depression, QoL, inflammation and oxidative stress</td>
<td>Probiotics had beneficial effects on depression and markers of oxidative stress and inflammation in individuals post-MI with a PCI Compared with placebo, Beck Depression Inventory score decreased (−5.57 versus −0.51, P = 0.045) and QoL increased (23.6 versus 0.44, P = 0.023) Total antioxidant capacity increased in the probiotic group (93.7 versus 2754 mmol/l, P = 0.009) and malondialdehyde (−40.7 versus −4.2, P = 0.023) and hs-CRP (−1.74 versus 0.67 mg/l, P = 0.04) decreased, with levels stronger than placebo</td>
<td>Small sample size Short supplementation duration Sample was predominantly male</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; DASS, Depression, Anxiety, and Stress Scale scores; GHQ, General Health Questionnaire; hs-CRP, high-sensitivity C-reactive protein; LGG, Lactobacillus rhamnosus GG; MI, myocardial infarction; PCI, percutaneous intervention; QoL, quality of life; RCT, randomised-controlled trial.

**Attention-deficit hyperactivity disorder and Asperger’s syndrome**

<table>
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<tbody>
<tr>
<td>Partty et al. 145</td>
<td>To determine the involvement of the gut-brain axis in the incidence of ADHD and AS in a cohort followed until 13 years old</td>
<td>LGG 1 × 10^8 CFU/day versus placebo to pregnant women 4 weeks before expected delivery, and then 6 months post-delivery to the infant Follow-up for 13 years</td>
<td>75 mothers and children</td>
<td>Clinical diagnosis of ADHD and AS</td>
<td>LGG supplementation in early life may reduce the risk of developing ADHD or AS By age 13 years, 6 children developed ADHD or AS or both, all of which were in the placebo group (P = 0.008) At 6 months old, numbers of Bifidobacterium were less in children with neuropsychiatric disorder than those without (P = 0.03) At 18 months old, Bacteroides and Lactobacillus-Enterococcus group were less in children with neuropsychiatric disorder (P = 0.008 and P = 0.01, respectively)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit hyperactivity disorder; AS, Asperger’s syndrome; CFU, colony-forming units; LGG, Lactobacillus rhamnosus GG; RCT, randomised-controlled trial.
### Urinary tract infections

<table>
<thead>
<tr>
<th>Author et al</th>
<th>Objective</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Coldner et al</td>
<td>To determine the vaginal colonisation in post-menopausal women by LGG</td>
<td>100 ml yoghurt daily containing 1 × 10^9 CFU LGG or 200 ml yoghurt daily containing 1 × 10^9 CFU LGG, 1 month</td>
<td>42 post-menopausal women</td>
<td>Colonisation count in vaginal and rectal swabs</td>
<td>LGG has a low vaginal adhesion rate and is not a good probiotic for UTIs. The vaginas of only 4 women (9.5%) were colonised with LGG, but 33 women (78.6%) had positive rectal swabs indicating GI colonisation</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kontiokari et al</td>
<td>To determine whether recurrent UTIs can be prevented with cranberry–lingonberry juice or with LGG</td>
<td>50 ml cranberry–lingonberry juice daily for 6 months versus 100 ml LGG drink (4 × 10^9 CFU) 5 times per week for 1 year versus no intervention</td>
<td>150 women with UTIs caused by Escherichia coli</td>
<td>First recurrence of UTI</td>
<td>Regular consumption of cranberry juice but not LGG prevents the recurrence of UTIs. Rate of first UTI recurrence differed between the groups (P = 0.014). Recurrent UTIs in 16% of women in cranberry group, 39% of women in LGG group and 36% of women in control. Difference between cranberry juice and control 20% reduction in absolute risk (95% CI: 3.5–5%, P = 0.023, NNT = 5.95)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Ng et al</td>
<td>To determine whether <em>Lactobacillus</em> spp. can prevent recurrent UTIs in females</td>
<td>9 clinical trials with 726 patients</td>
<td>Prophylactic efficacy and incidence of adverse events</td>
<td>The use of <em>Lactobacillus</em> spp. reduced the risk of recurrent UTIs (RR = 0.684, 95% CI: 0.43–0.929, P ≤ 0.001). However, different strains showed varying efficacy</td>
<td>Inter-study variability and short treatment durations</td>
<td></td>
</tr>
<tr>
<td>Sadeghi-Bojd et al</td>
<td>To determine the efficacy of multispecies probiotic for the prevention of recurrent UTIs in children</td>
<td>LGG 1 × 10^9 CFU + <em>Lactobacillus acidophilus</em> 15 × 10^9 CFU + <em>Bifidobacterium bifidum</em> 4 × 10^9 CFU + <em>Bifidobacterium lactis</em> 15 × 10^9 CFU</td>
<td>181 children with normal urinary tracts given LGG + <em>L. acidophilus, B. bifidum, B. lactis</em> versus placebo, 18 months</td>
<td>Composite cure at 18 months</td>
<td>Multispecies probiotic more effective at reducing the risk of recurrent UTIs. Composite cure in probiotic 96.7% versus 83.3% placebo (P = 0.02). Time to first recurrent event was 3.5 months in probiotic group and 6.5 months in placebo group (P = 0.04)</td>
<td>Patients from a limited selection pool. Did not include uncircumcised boys. Did not test to see if supplementation reduced GI colonisation by pathogenic bacteria</td>
</tr>
<tr>
<td>Toh et al</td>
<td>To determine the efficacy of intravesical LGG on urinary symptoms in individuals with spinal cord injury</td>
<td>Four arms: (i) <em>Lactobacillus reuteri</em> RC-14 + <em>Lactobacillus rhamnosus</em> GR-1 (5.4 × 10^9 CFU) + LGG–Bifidobacterium animalis BB-12 (7 × 10^9 CFU); (ii) RC-14–GR-1 (conc. as above) + placebo; (iii) LGG–BB-12 (conc. as above) + placebo; (iv) placebo + placebo, 6 months</td>
<td>207 individuals with spinal cord injury</td>
<td>Occurrence of first symptomatic UTI</td>
<td>No effect of either probiotic combination for preventing UTIs in people with spinal cord injury. RC-14–GR-1 had a similar risk of UTI to placebo (HR 0.67, 95% CI: 0.39–1.18), and those on LGG–BB-12 also had a similar risk to those on placebo (HR 1.29, 95% CI: 0.74–2.25, P = 0.37)</td>
<td>Did not recruit the target number of 372 participants. No trial follow-up</td>
</tr>
<tr>
<td>Tractenberg et al</td>
<td>To determine the efficacy of intravesical LGG on urinary symptoms in individuals with spinal cord injury</td>
<td>Self-administration of a catheter with LGG + saline (2 × 10^9 CFU live organisms)</td>
<td>96 adults and 7 children with spinal cord injury</td>
<td>Change in USQNB-IC</td>
<td>Intravesical administration of LGG improved symptoms of UTIs compared with individuals who did not administer the probiotic (P ≤ 0.005)</td>
<td>No randomisation</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; LGG, *Lactobacillus rhamnosus* GG; NNT, number needed to treat; RCT, randomised-controlled trial; RR, relative risk; USQNB-IC, Urinary Symptom Questionnaire for Neurogenic Bladder-IC; UTI, urinary tract infection.
### Infant health

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Chrzanowska-Liszewska et al. [67] Poland RCT</td>
<td>To determine the colonisation of LGG and its impact on growth and length of hospital stay in pre-term infants</td>
<td>LGG 6 × 10⁸ CFU/day versus placebo, 42 days</td>
<td>60 pre-term infants before 32 weeks</td>
<td>Difference in the amount of Bifidogenic microflora and Escherichia coli</td>
<td>Although LGG rapidly colonised the gut of preterm formula-fed infants, this did not decrease the number of pathogenic bacteria or affect growth. LGG was higher in supplemented group than placebo at days 7 (P = 0.041) and 21 (P = 0.024). Staphylococci were higher in supplemented group at days 7 (P = 0.001) and 42 (P = 0.011). No difference in weight gain (95% CI: −168.3, 305.5, P = 0.567) or mean hospital duration (95% CI: −13.43, 5.71, P = 0.421).</td>
<td>Lack of follow-up; No precise CFU count for organisms analysed.</td>
</tr>
<tr>
<td>Luoto et al. [77] Finland Follow-up of RCT</td>
<td>To determine the clinical benefit and safety of probiotics during the perinatal period Follow-up of 4 previous RCTs</td>
<td>Included trials were 3–6 months duration, and dosages ranged from 1 × 10⁹–1 × 10¹⁰ CFU, 2-year follow-up</td>
<td>303 children pre-term or increased allergy risk</td>
<td>Not stated</td>
<td>Children given LGG had a decreased prevalence of allergic disease compared with placebo (OR 0.62, 95% CI: 0.38–0.99, P = 0.047). No difference in prevalence of asthma (OR 0.55, 95% CI: 0.24–1.25, P = 0.15), non-communicable diseases or growth.</td>
<td>Follow-up completed unblinded.</td>
</tr>
<tr>
<td>Luoto et al. [77] Finland Follow-up of RCT</td>
<td>To determine the safety and efficacy of multispecies probiotic containing LGG on pregnancy outcome, and foetal and infant growth</td>
<td>Diet + LGG (1 × 10⁹ CFU/day) + Bifidobacterium lactis (1 × 10⁸ CFU/day) versus diet + placebo from first trimester to cessation of breastfeeding</td>
<td>256 pregnant women 191 completed the 24-month follow-up</td>
<td>Pregnancy outcome and infant growth</td>
<td>The use of probiotics in pregnancy could be safe and cost-effective to prevent future metabolic disease. Probiotics + diet reduced the frequency of gestational diabetes (P ≤ 0.003).</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Vendt et al. [65] Estonia RCT</td>
<td>To determine the effect of LGG-enriched formula on growth and faecal microflora in the first 6 months of healthy infants</td>
<td>LGG dosage not stated, 6 months</td>
<td>120 healthy infants</td>
<td>Not stated</td>
<td>Infants fed with LGG-supplemented formula grew better than those with regular formula. Length and weight higher in supplemented group versus control (0.44 ± 0.37 vs. 0.07 ± 0.06, P = 0.01 and 0.44 ± 0.19 vs. 0.07 ± 0.06, P = 0.005). More frequent colonisation amongst supplemented formula group (91% vs. 76%, P &lt; 0.05). More frequent defecation in LGG group (61 ± 2.6 vs. 8.0 ± 2.8, P &lt; 0.05).</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Mantaring et al. [66] Philippines RCT</td>
<td>To determine the effect of probiotics during pregnancy and early lactation on infant diarrhoea</td>
<td>LGG 7 × 10⁸ CFU + B. lactis 7 × 10⁸ CFU per day versus control</td>
<td>208 healthy pregnant women in third trimester</td>
<td>Incidence of infant diarrhoea until age 12 months</td>
<td>Maternal supplementation showed beneficial effects on infant weight and length gain; however, did not affect incidence of infant diarrhoea. Weight and height increased compared with placebo (8.97 kg versus 8.61 kg, P = 0.001 and 44 cm versus 43.7 cm, P = 0.31).</td>
<td>Limited generalisation; Diet and exercise not considered.</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; LGG, *Lactobacillus rhamnosus* GG; OR, odds ratio; RCT, randomised-controlled trial.
## Infantile colic

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Intervention period, treatment dose</th>
<th>Number of subjects</th>
<th>Main outcome measure</th>
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<tbody>
<tr>
<td>Cabana et al.²⁴</td>
<td>To determine whether LGG supplementation prevents infant colic</td>
<td>LGG 1 × 10⁹ CFU/day versus control, 6 months</td>
<td>184 infants</td>
<td>Likelihood of diagnosis of colic before 4 months old</td>
<td>Early LGG supplementation does not prevent infant colic. No difference between two groups in infants with colic based on symptoms (control 5.4% versus LGG 9.8%, P = 0.019) or physician diagnosis (control 3.2% versus LGG 7.6%, P = 0.26) or combination of both (6.5% versus LGG 13.0%, P = 0.013)</td>
<td>Parent report of symptoms and crying length. High rate of breastfeeding in sample may mask effects of probiotic. Samples were not racially or socially diverse.</td>
</tr>
<tr>
<td>Kianifar et al.²⁷</td>
<td>To determine efficacy of multispecies probiotic and prebiotic to reduce crying time</td>
<td>1 × 10⁸ CFU Lactobacillus casei + LGG + Streptococcus thermophilus + Bifidobacterium breve + Lactobacillus acidophilus + Bifidobacterium infantis + Lactobacillus bulgaricus + fructo-oligosaccharide versus placebo, 30 days</td>
<td>50 breastfed infants</td>
<td>Treatment success</td>
<td>Symbiotic significantly improved colic symptoms compared with placebo. At day 7 and day 30, treatment success was higher in symbiotic compared with placebo (day 7, 82.6% versus 35.7%, P ≤ 0.005; day 30, 87% versus 46%, P = 0.01). Symptom resolution higher in symbiotic group at day 7 (39% versus 7%, P = 0.03) but not day 30 (56% versus 36%, P = 0.24)</td>
<td>Stool samples not evaluated at baseline or after intervention. Small sample size. Non-validated outcome measure. No measure of compliance.</td>
</tr>
<tr>
<td>Partty et al.²⁷²</td>
<td>To determine the efficacy of LGG to reduce daily crying of infants with colic</td>
<td>LGG 4.5 × 10⁹ CFU/day versus placebo, 4 weeks</td>
<td>17 healthy breastfed infants under 6 weeks old</td>
<td>Difference in daily average crying time between LGG and placebo</td>
<td>LGG in combination with behavioural support and cow’s milk elimination was not efficacious for the reduction of crying time in infants with colic. Daily crying time comparable between the groups (173 minutes probiotic versus 174 minutes placebo, P = 0.99). However, occurrence of crying decreased in the probiotic group compared with placebo (68% versus 49%, 95% CI: 32–66, P = 0.05)</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Savino et al.²⁷³</td>
<td>To determine the efficacy of LGG together with maternal avoidance of cow’s milk in treating infantile colic</td>
<td>LGG 5 × 10⁹ CFU/day versus placebo, 28 days</td>
<td>45 colicky breastfed infants</td>
<td>Faecal CLP, crying and fussing</td>
<td>LGG in combination with elimination of cow’s milk from maternal diet reduced crying time (104 minutes versus 242 minutes, P ≤ 0.001) and faecal CLP (P = 0.026), and increased total gut bacteria (P = 0.04) and Lactobacillus (P = 0.048)</td>
<td>Possible false-positive with the use of PCR test. Small sample size.</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; CLP, calprotectin; LGG, Lactobacillus rhamnosus GG; PCR, polymerase chain reaction; RCT, randomised-controlled trial.

## Human immunodeficiency virus

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<tr>
<td>Salminen et al.²⁷⁵</td>
<td>To determine the efficacy and safety of LGG for GI symptoms in patients with HIV on anti-retroviral therapy</td>
<td>LGG 1–5 × 10⁹ CFU twice daily versus placebo, 2 weeks</td>
<td>17 HIV-infected patients with diarrhea for more than 1 month</td>
<td>GI symptoms Safety parameters Faecal microbiology</td>
<td>LGG supplementation was well tolerated, but showed no benefits to diarrhoea or GI symptoms in HIV-infected patients. No differences between faecal counts of LGG between supplemented and placebo. No adverse events reported</td>
<td>Not stated.</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; GI, gastrointestinal; HIV, human immunodeficiency virus; LGG, Lactobacillus rhamnosus GG; RCT, randomised-controlled trial.
**Allergy**

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<tr>
<td>Tan et al.190</td>
<td>To determine the effects of LGG in children with CMA</td>
<td>LGG dosages ranged from 1.4 × 10^7 CFU to 5 × 10^8 CFU/day, with treatment durations from 4 weeks to 3 years</td>
<td>10 studies 853 children</td>
<td></td>
<td>LGG may have moderate-quality evidence to promote tolerance and aid recovery from GI symptoms in children with CMA. Higher tolerability rates favouring LGG over controls were observed (RR = 2.22, 95% CI: 1.86–2.66, I^2 = 0.00, moderate-quality evidence). No significant differences in SCORAD values (MD 141, 95% CI: −4.99, 782, P = 0.67, very low-quality evidence), and LGG may have improved faecal occult blood (RR = 0.36, 95% CI: 0.14–0.92, P = 0.03; low-quality evidence). No adverse events reported.</td>
<td>Limited number of studies</td>
</tr>
<tr>
<td>Korpela et al.186</td>
<td>To determine whether multispecies probiotic could ameliorate antibiotic use or Caesarean birth on infant gut microbiota</td>
<td>LGG (5 × 10^8 CFU) + Bifidobacterium breve Bb99 (2 × 10^8 CFU) + Propionibacterium freudenreichii spp. shermani JS (2 × 10^8 CFU) + Lactobacillus rhamnosus Lc705 (5 × 10^8 CFU) versus placebo</td>
<td>199 breastfed or formula-fed infants</td>
<td></td>
<td>LGG supplementation may ameliorate changes in the gut microbiota due to antibiotic use or Caesarean birth</td>
<td></td>
</tr>
<tr>
<td>Piirainen et al.193</td>
<td>To determine the effects of LGG on oral immune response of adults with birch pollen allergy</td>
<td>LGG (2 × 10^10 CFU/day) versus placebo</td>
<td>38 birch pollen allergy sufferers</td>
<td></td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Moreira et al.194</td>
<td>To determine the effect of LGG supplementation on allergic inflammatory markers in marathon runners with asthma and allergy</td>
<td>LGG (3 × 10^8 CFU/day) versus placebo</td>
<td>141 marathon runners with allergies</td>
<td></td>
<td>Compared with placebo, LGG supplementation did not prevent an increase in allergic markers during birch pollen season</td>
<td></td>
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</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; CMA, cow’s milk allergy; GI, gastrointestinal; LGG, *Lactobacillus rhamnosus* GG; MD, mean difference; RCT, randomised-controlled trial; RR, relative risk; SCORAD, Scoring of Atopic Dermatitis.

**Dermatitis and eczema**

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<tr>
<td>Szajewska &amp; Horváth193</td>
<td>To determine the efficacy of LGG prenatally/postnatally for the primary prevention of eczema</td>
<td>LGG dosages ranged from 1 × 10^9 CFU to 1.8 × 10^10 CFU</td>
<td>5 RCTs 889 subjects</td>
<td></td>
<td>LGG was ineffective in reducing eczema, and guidelines should be revised to reflect this (1 RCT: RR = 0.88, 95% CI: 0.63, 122, P = 0.69, F = 0%) No reduction of risk for eczema when LGG administered during pregnancy (3 RCTs, RR = 0.93, 95% CI: 0.49, 176, F = 72%) No reduction of risk when LGG administered to infants (1 RCT: RR = 0.93, 95% CI: 0.59, 145)</td>
<td>Different trials used different definitions of eczema</td>
</tr>
</tbody>
</table>
**Schmidt et al.** 2013

Denmark

**RCT**

To determine the effect of multispecies probiotic in late infancy and early childhood on the development of allergic diseases

LGG + Bifidobacterium animalis spp. lactis versus placebo, 6 months

290 participants starting prior to attending day care

Incidence of allergic disease

Probiotics administered in late infancy may prevent the development of eczema. Incidence of eczema was 4.2% in probiotic group and 5% in eczema group (P = 0.036)

Study set from a previous trial of high-income families

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**Tan-Lim et al.** 2012

Philippines

Systematic review and meta-analysis

To determine the effect of multispecies probiotics in prevention of AD in children

LGG + B. animalis

21 RCTs, 5406 children with AD

Incidence of allergic disease

Specific probiotics reduce the risk of dermatitis in children when administered in utero, during infancy or both. Reduced risk of AD (RR = 0.50, 95% CI: 0.27−0.94) compared with placebo. LGG had less adverse events compared with placebo (RR = 0.70, 95% CI: 0.32−1.52) in infants. Reduced risk of AD (RR = −0.46, 95% CI: 0.22−0.97). All based on low-quality evidence

When ranking evidence, quality not considered

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**Wu et al.** 2013

Taiwan

**RCT**

To determine the efficacy and safety of LGG in children aged 4–48 months with AD

LGG (ComProbi brand containing 350 mg) versus control, 8 weeks

67 children aged 4–48 months with AD

Mean change from baseline in SCORAD at 8 weeks

LGG was effective to decrease symptoms of AD compared with placebo (P ≤ 0.05)

Lack of laboratory assessment

Patients could use topical steroids

Unethical to withhold corticosteroid treatment

Lack of follow-up

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Ade, atopic dermatitis; CFU, colony-forming units; CI, confidence interval; LGG, *Lactobacillus rhamnosus GG*; RCT, randomised-controlled trial; RR, relative risk; SCORAD, Scoring of Atopic Dermatitis.

### Wounds

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<tbody>
<tr>
<td>Mayes et al.</td>
<td>To determine the efficacy and safety of LGG supplementation in acutely burned, paediatric patients</td>
<td>LGG 1.5 × 10^10 CFU/day versus placebo within 10 days of burn until wound closure</td>
<td>20 acutely burned paediatric patients</td>
<td>Not stated</td>
<td>No difference between infection days, length of hospitalisation or antibiotic use</td>
<td>Time required to complete wound healing shortened with LGG but not significant</td>
</tr>
</tbody>
</table>

**CFU, colony-forming units; LGG, *Lactobacillus rhamnosus GG*; RCT, randomised-controlled trial.**

### Dental caries

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<tbody>
<tr>
<td>Nase et al.</td>
<td>To determine whether milk containing LGG had an effect on caries and caries risk in children</td>
<td>LGG (5–10 × 10^5 CFU/ml) versus control 5 days per week for 7 months</td>
<td>594 children</td>
<td>Not stated</td>
<td>LGG reduced the risk of caries (OR 0.56, P = 0.01), an effect that was pronounced in 3–4-year-olds</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

**CFU, colony-forming units; LGG, *Lactobacillus rhamnosus GG*; OR, odds ratio; RCT, randomised-controlled trial.**
## Vaccine adjuvant

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<tr>
<td>Bianchini et al.</td>
<td>To determine whether LGG can modify immune response in children and adolescents with T1D leading to an increased immune response to the influenza vaccine</td>
<td>LGG 1 \times 10^9 CFU per day versus placebo. Three months prior and post vaccination.</td>
<td>64 paediatric patients with T1D</td>
<td>Seroconversion rate</td>
<td>Combination of vaccine and LGG reduced the inflammatory response without dampening seroprotective antibodies. IL-17 significantly lower in LGG ((P&lt;0.01))</td>
<td>Small study size</td>
</tr>
<tr>
<td>De Vrese et al.</td>
<td>To determine whether and how probiotics affect the immune response following polio vaccine</td>
<td>LGG 1 \times 10^9 CFU or <em>Lactobacillus acidophilus</em> CRL431 \times 10^10 CFU/serving in milk versus placebo. 5 weeks</td>
<td>66 healthy males</td>
<td>Not stated</td>
<td>Probiotics induce an immune response that may provide enhanced protection from viruses. LGG or CRL431 nearly doubled the increase in polio-specific IgG ((P&lt;0.01)) IgA titre increases after vaccination ((P \leq 0.036))</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lazarus et al.</td>
<td>To determine the effect of probiotics and/or zinc supplementation on the immune response to rotavirus vaccination</td>
<td>4 arms: LGG (1 \times 10^{10} CFU) + zinc sulphate; 5 mg probiotic + placebo; zinc + placebo; placebo + placebo. Duration not stated.</td>
<td>620 infants given rotavirus at 6 and 10 weeks old</td>
<td>Seroconversion to rotavirus at 14 weeks old</td>
<td>Zinc supplementation did not improve immunogenicity of rotavirus vaccine, and probiotic supplementation only marginally increased seroconversion. No changes to seroconversion in zinc arm and only modest improvement among infants receiving probiotic ((P = 0.066))</td>
<td>Absence of immune correlate of protection for rotavirus vaccine</td>
</tr>
<tr>
<td>Davidson et al.</td>
<td>To determine the effects of LGG as an immune adjuvant to increase rates of seroconversion after influenza vaccine</td>
<td>LGG 1 \times 10^9 CFU + inulin twice daily versus placebo twice daily. 28 days</td>
<td>42 healthy adults</td>
<td>Protective HAI assay</td>
<td>LGG may be an important adjuvant to improve immunogenicity following influenza vaccine. No LGG well tolerated. No differences in seroprotection of H1N1 and B influenza strains. Increased protective titre with LGG following H3N2 strain vaccine (OR 1.84, 95% CI: 1.04−3.22, (P = 0.048))</td>
<td>Small sample size. Subjects previously vaccinated were included</td>
</tr>
</tbody>
</table>

CFU, colony-forming units; CI, confidence interval; HAI, haemagglutinin inhibition; IL, interleukin; LGG, *Lactobacillus rhamnosus* GG; OR, odds ratio; RCT, randomised-controlled trial; T1D, type 1 diabetes.
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