

Systematic Review

Probiotic Interventions in Coeliac Disease: A Systematic Review with a Focus on Cardiovascular Risk

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Abstract: People with coeliac disease (CD) have a higher risk of developing cardiovascular disease (CVD), potentially due to inflammation. Probiotics can influence CVD risk through several mechanisms including modifying inflammation. We performed a systematic review of probiotic interventions in people with CD. In total, 4 databases were systematically searched for studies published up to March 2023. All outcomes, inclusive of any cardiovascular risk factors, were collated and reported. We screened 8084 articles and 11 publications reporting on 7 RCTs and 2 non-RCTs met the inclusion criteria for qualitative analysis. In total, 1 RCT and both non-RCTs were considered to have a high risk of bias. There was large heterogeneity between the studies and adherence to a gluten-free diet was only measured in two studies. No specific outcomes related to cardiovascular risk were reported. Two studies reported a significant reduction on serum TNF- α in children over time after probiotic supplementation. One study reported no significant change in intestinal permeability over a 3-week intervention. Currently there is insufficient evidence to advocate a positive impact of probiotics on inflammation in CD, due, in part, to the limited data on adherence to the gluten-free diet and active disease.



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1. Introduction

Coeliac disease (CD) is a chronic inflammatory bowel condition, triggered by an autoimmune response which is characterized by a permanent sensitivity to gluten in genetically predisposed people [1]. The small intestines are primarily affected at the onset and duration of the disease, however, there are broad clinical manifestations usually presenting as both intestinal and extraintestinal symptoms. Gluten is the term used for storage proteins derived from cereal grains barley, rye, and wheat. The prevalence of CD is steadily increasing with approximately 1% of people affected in the world's population [2]. With no cure, lifelong adherence to a gluten-free diet (GFD) (a combination of naturally gluten-free and processed foods comprising less than 20 ppm gluten) is recognized as the only effective treatment for CD [3]. Adhering to a GFD can be very challenging; it requires knowledge, skills and modified behaviours to undertake the substantial changes to dietary habits [4].

The gut microbiota, which is a complex community of microorganisms, within people with CD differs compared with controls, whether this CD-associated dysbiosis is the consequence of the inflammation or a concurring causative factor remains to be established [5]. Intestinal dysbiosis persists on the GFD, which itself can contribute due to the reduced fibre content [6,7]. Dysbiosis has been associated with cardiovascular disease (CVD), through several mechanisms including microbiota-derived metabolites [8,9]. People with CD are more likely to develop atherosclerosis, likely as a result of systemic inflammation and low

high-density lipoprotein levels that may contribute to atherosclerosis [10,11]. It has been reported that a third of patients with CD adhering to a GFD had concurrent non-alcoholic fatty liver disease (NAFLD), accounting for a three-fold increased risk compared with the general population [12]. Conroy et al. (2023) report, analysis from UK Biobank data, people with CD have a higher risk of developing cardiovascular disease than did people with no coeliac disease [13].

Studies have suggested a GFD itself may also contribute to metabolic syndrome and hyperlipidaemia observed in people with CD [14–18], with significantly more saturated fat in GF compared with gluten containing counter parts [19]. Based on findings from a large epidemiological study, Lebwohl et al. (2017) suggest the avoidance of gluten may result in reduced consumption of beneficial whole grains, which may affect cardiovascular risk [20]. A systematic review of studies up to 2021, indicated there was insufficient evidence to link a GFD with CVD, however, there was considerable heterogeneity within the studies [21].

The gut microbiota has an essential role in regulating lipid absorption in the human intestine [9]. Two studies reported participants consuming *Lactobacillus plantarum* ECGC 13110402 (LP_{LDL}[®]) supplement, exhibited reductions in their LDL-cholesterol and increased HDL Cholesterol [22,23]. Derosa et al. (2020) reported significant reductions were seen in blood pressure and level of LDL cholesterol after three months of LP_{LDL}[®] [24]. They concluded that major risk factors for cardiovascular events such as high blood pressure and hypercholesterolemia could be managed with a probiotic [24].

Previous literature reviews on probiotics in coeliac disease have reported their potential role in inflammation and gastrointestinal symptoms [25,26]. We performed a systematic review of the literature to evaluate the effects of probiotic interventions in people with CD to collate knowledge from all outcomes inclusive of any cardiovascular risk factors.

2. Results

Records identified through initial literature search were 9672 in total. This number was reduced to 8084 after duplicates were removed. As shown in the flow chart (Figure 1) we reviewed thirty-one full-text studies. Upon further review, we excluded twenty studies, and the remaining eleven publications met the inclusion criteria and were eligible for qualitative synthesis which is summarised in Table 1.

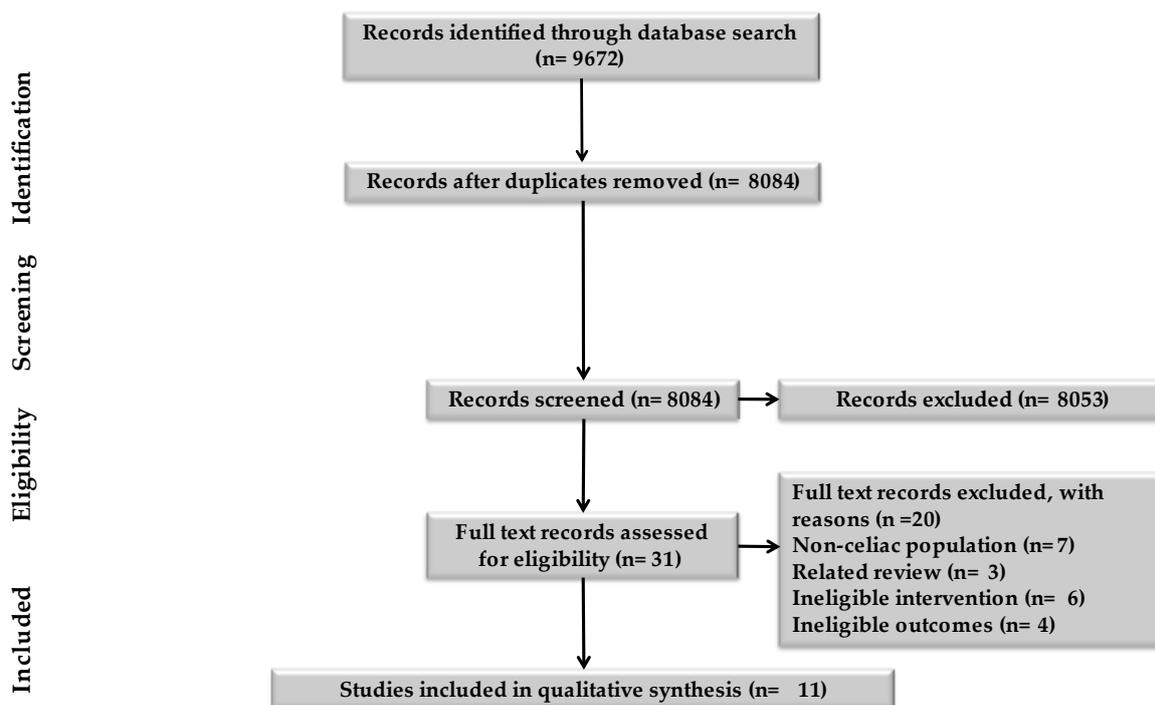


Figure 1. Flow Chart of Study Selection.

2.1. Characteristics of Studies

All studies included were in English and did not require translation. We performed analysis on 11 reports [27–41] including 7 RCTs with a total of 618 participants. In total, 3 articles reported the findings from 1 RCT [29,31,34]. All studies included were published from 2013 to 2022. The studies were conducted in medical centres with 2 studies from Argentina, 1 from Spain, 1 from Australia, 1 from Brazil, 1 from Italy, 1 from Pakistan and 3 from Slovenia. The 3 Slovenian reports had a common intervention cohort from which three publications reported outcomes [29,31,34]. The majority of all participants from the studies were female, 6 studies included adults whereas 3 studies (5 publications) included only children.

Four studies reported only faecal analysis from their participants [35,37,39,41], whilst one reported blood analyses only [29]. Five studies conducted both faecal and blood analyses [27,28,30,34,36]. One study reported a duodenal biopsy analysis only [32]. The probiotic strains and dosages were the same for the three publications of the Slovenia cohort as well as the two Argentina studies but were different in all other studies. Six studies monitored adverse events [27–30,35,36] comparing probiotics to placebo no differences in the number of adverse events were reported. All except one RCT used either a placebo capsule or sachet with the one RCT [37] did not use a placebo for their controlled study. Every study excluded participants who were on any medications including antibiotics and immunosuppressants as they could have had effects on the outcome. Studies also excluded participants who had severe malnutrition, organic disorders, or suspicion of cancer.

Most reports, except four [27,28,32,37], participants had been diagnosed of coeliac disease by serologic testing and had been on a GFD for over 6 months before starting in the study. Persistent symptoms in participants were reported in three studies while on a GFD [30,35,36]. Francavilla et al., reported participants had an additional diagnosis of irritable bowel syndrome [35]. The studies undertaken by Ali et al. and Olivares et al. included newly diagnosed children who started a GFD for the study [28,37] and one study included newly diagnosed adults who were on a GFD with no other comorbidities [27]. Only two studies monitored the adherence to a GFD [28,30] even though for all other studies it was a pre-requisite to be on GFD in order to be included in the study. Olivares et al. used the 72 h food diary whilst Harnett et al. used the 3-day food diary.

2.2. Risk of Bias Assessment

Five RCTs were considered to have a low risk of bias, three with some concerns and one with high risk of bias; details for each domain can be found within Table 1. Full details of subcategories within Supplementary Materials in Tables S1 and S2. Both non-RCTs were considered to have a high risk of bias; details for each domain can be found in Table 2. The domain ‘measurement of outcomes’ was analysed for two outcomes: For gastrointestinal symptoms, four reports were judged as LOW risk of bias [27,28,35,36] whilst one had a HIGH risk of bias [37]. For inflammatory markers, three studies measured this outcome and were judged as LOW risk of bias [27,29–33].

Table 1. Risk of bias for Randomised Controlled Trials.

	Randomisation Process	Deviations from Intended Intervention	Missing Outcome Data	Measurement of Outcome Gastro Symptoms	Measurement of Outcome Inflammation	Selection of Reported Results	Overall
Smecuol et al., 2013 [27]	Low	Some concerns	Low	Low	Low	Low	Some concerns
Olivares et al., 2014 [28]	Low	Some concerns	Low	Low	Low	Low	Some concerns
Klemenak et al., 2015 [29]	Low	Some concerns	Low	Not measured	Low	Low	Low risk of bias
Harnett et al., 2016 [30]	Low	Some concerns	Low	Not measured	Not measured	Low	Low risk of bias
Quagliariello et al., 2016 [31]	Low	Some concerns	Low	Not measured	Not measured	Low	Low risk of bias

Table 1. Cont.

	Randomisation Process	Deviations from Intended Intervention	Missing Outcome Data	Measurement of Outcome Gastro Symptoms	Measurement of Outcome Inflammation	Selection of Reported Results	Overall
Primec et al., 2019 [34]	Green	Orange	Green	Not measured	Not measured	Green	Low risk of bias
Francavilla et al., 2019 [35]	Green	Green	Green	Green	Not measured	Orange	Low risk of bias
Smecuol et al., 2020 [36]	Orange	Orange	Orange	Green	Not measured	Orange	Some concerns
Ali et al., 2022 [37]	Orange	Orange	Green	Red	Not measured	Red	High risk of bias

Green: Low risk of bias; Orange: Some concerns; Red: High risk of bias. Full details of subcategories within supplementary information.

Table 2. Risk of bias for Non-Randomised Controlled Trials.

Non RCTs	Bias Due to Confounding	Bias in Selection of Participants into the Study	Bias in Classification of Interventions	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
Pinto-Sanchez et al., 2016 [32]	Orange	Red	Green	Red	Green	Red	Green	High risk of bias
Martinello et al., 2017 [33]	Orange	Green	Red	Green	Green	Red	Green	High risk of bias

Green: Low risk of bias; Orange: Some concerns; Red: High risk of bias. Full details of subcategories within supplementary information.

2.3. Impact of Probiotic Intervention on Outcomes

The Effects of Probiotics on Gut Microbiota: Eight studies conducted faecal analysis but only four measured the microbiota composition and reported data for absolute abundance inclusive of bifidobacterial and lactobacilli species [28,30,31,35]. One of the four studies reported significant increases in bifidobacteria species after probiotic intervention when compared to placebo and no significant increase was observed in the lactobacilli species. Only two studies out of the four had lactobacilli as part of their formulations, however, the counts of the lactobacilli species were not high.

The Effect of Probiotics on Cardiovascular Risk Factors: None of the studies reported outcomes on cardiovascular risk factors (Tables 3 and 4). Inflammatory markers: Two studies assessed the effects of probiotics on serum TNF- α in children (Tables 3 and 4). In the Klemenak et al. study, participants had been on a GFD for at least 6 months, they reported a significant reduction over time [29]. Whereas patients in Olivares et al. study patients started the GFD simultaneously with probiotics, a potential trend towards a reduction in TNF- α was observed [28]. One study reported intestinal permeability with the use of lactulose/mannitol ratio intestinal permeability test [27]. No change in intestinal permeability was observed over the 3-week intervention.

The Effect of Probiotics on the Quality of Life (QoL): Only two studies reported outcomes for QoL (Tables 3 and 4). Francavilla et al. used the validated irritable bowel syndrome-QoL questionnaire tool (IBS-QoL) and Harnett et al. used the validated coeliac disease questionnaire tool (CDQ). In both studies, QoL scores after treatment did not differ between probiotic and placebo treatments [30,35].

Table 3. Characteristics of studies and reported outcomes for RCTs.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Smecuol et al., 2013 [27] Argentina DBRCT	Probiotic: 12 Placebo: 10	M/F: 4/18 Probiotic: Age 46 (29–62) years Placebo: Age 40 (20–71) years Dx: active CD, on gluten containing diet before GFD. No other active chronic gastrointestinal pathologies No additional diagnosis. Blood and urine sample analysed.	<i>B. infantis</i> NLS super strain (2×10^9 Colony-Forming Units) vs. Placebo, 3 times per day, 15 min before meals 5 g of lactulose and 2 g of Mannitol in 450 mL of water for fractional excretion ratio	2-week run -in, 3-week treatment, 50-day f/u to initiate GFD	Quality of life: None reported. Gastro Symptoms: bloating and abdominal distention (20/22), abdominal pain (19/22), diarrhoea (11/22) for both groups Markers of active disease: Probiotics: Reduction in serum antibody concentrations (10% for IgA tTG and IgA DGP antibodies) Placebo: Increased antibody serum concentrations (IgA tTG, 7% and IgA DGP, 10%) at the end of the trial. Biochemical and microbial data: Primary endpoint: Non-significant increase of mean lactulose/mannitol ratio from baseline for the probiotic ($p = 0.064$) and placebo ($p = 0.342$) and Secondary endpoint: Probiotic: significant reduction in indigestion ($p = 0.0035$) and constipation ($p = 0.0483$) symptoms, however, borderline for reflux symptoms ($p = 0.0586$). Placebo: No significant changes in any syndrome (indigestion, diarrhoea, constipation, abdominal pain). Significant improvement in diarrhoea symptoms Outcome of inflammatory mediators: Probiotic and placebo: No significant changes in Th1 serum cytokines and serum chemokines. Significant increase in high baseline serum concentration of MIP-1 β , ($p < 0.04$), but not in the placebo group. Cardiovascular risk factors: None reported.

Table 3. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Olivares et al., 2014 [32] Spain DBRCT	Probiotics: 17 Placebo: 16	Probiotic: Age 6.8 ± 0.9 years M/F (7/10) Placebo: Age 8.5 ± 1.2 years M/F (8/8) Dx: biopsy newly diagnosed CD. Adherence to GFD after diagnosis confirmation. Food records for 72 h (2 weekdays, 1 weekend day) before start and after 3 mnths intervention. No additional diagnosis. Blood and faecal sample analysed; DNA sequencing with QIAamp DNA stool Mini Kit and Real time PCR to quantify content of bacterial groups.	<i>Bifidobacterium longum</i> CECT 7347 (10^9 CFU) vs. Placebo At lunch time	3 months	Quality of life: Not reported. Gastro Symptoms: Self-reported improvements in diarrhoea, constipation, abdominal pain, and vomiting. No significant changes in both groups for energy intake other specific nutrients ($p > 0.05$). GFD adherence led to slight decrease in dietary fibre. Probiotic: higher mean increment in weight and height percentiles than in the placebo group. Markers of active disease: Probiotic: Decreases in $CD3^+$ ($p = 0.013$) and $HLA-DR^+$ ($p = 0.029$) T cell populations but no significant changes in placebo. No significant differences seen in T lymphocytes $HLA-DR^+$, $CD4^+$, $CD4^+Foxp3^+$ and $CD8^+$ for both groups ($p = 0.328$, $p = 0.970$, $p = 0.504$ and $p = 0.376$). Biochemical and microbial data: Slight reduction in serum $TNF-\alpha$ for probiotic group ($p = 0.067$); but difference between both groups was not significant ($p = 0.085$). No significant differences found in both groups for serum IL-10, interferon- γ , IL-13, transforming growth factor- $\beta 1$, IgG1 and IgG4. Placebo: Significant increase in gene copy <i>Bacteroides fragilis</i> group ($p = 0.013$), <i>Enterobacteriaceae</i> ($p = 0.038$), non-significant decrease in <i>Bifidobacterium</i> spp. ($p = 0.151$). Probiotic: No significant differences in <i>Lactobacillus</i> group, <i>Bifidobacterium</i> spp./ <i>B. fragilis</i> group and Enterobacteriaceae. Significant decrease in faecal slgA concentration Cardiovascular risk factors: None reported.
Slovenia RCT 3 publications					

Table 3. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Klemenak et al., 2015 [33] Slovenia DBRCT	49 patients Placebo: 24 Probiotic: 22 HC: 18	Placebo: Age 10.81 ± 5.0 years, M/F (10/14) Time on GFD 7.1 ± 5.5 years, Compliance on GFD (80%) Probiotic: Age 10.4 ± 4.2 years M/F (6/16) Time on GFD 5.6 ± 3.7 years, HC: Age 8.8 ± 6.0 years M/F (7/11) Dx: biopsy On GFD from 0.5 to 15 years. No additional diagnosis. Compliance on GFD (91%) in probiotic group and 80% in placebo Blood sample analysed.	Lyophilized 50% <i>B. breve</i> BR03 (10^9 CFU) and 50% <i>B. breve</i> B632 (10^9 CFU) vs. Placebo Daily at breakfast	3 months; 3 months f/u	Quality of life: None reported. Gastro Symptoms: None reported. Markers of active disease: None reported. Biochemical and microbial data: TNF- α in serum at baseline, significantly higher ($p = 0.015$) in the probiotic group (14.78 ± 6.43) than placebo group (10.58 ± 3.57). TNF- α in serum at the end of the study, significant decrease ($p = 0.020$) in the probiotic group (11.97 ± 3.58) from baseline levels. TNF- α in serum on f/u, significantly higher in the probiotic group No correlation between positive serologic markers of CD and levels of TNF- α and IL-10 in individual patient with CD. Values for cytokine IL-10 in serum, below assay detection limit (5 pg/mL) and so not analysed. Cardiovascular risk factors: None reported.
Quagliariello et al., 2016 [35] Slovenia DBRCT	Probiotic: 20 Placebo: 20 HC: 16	Age 1–19 years Dx: biopsy On GFD for at least 3 months. No additional diagnosis. Faecal sample analysed; DNA extraction and sequencing with QIAamp DNA stool Mini Kit and molecular analyses; absolute quantification using Quantitative PCR.	<i>B. breve</i> BR03 (DSM 16604) (10^9 CFU) and <i>B. breve</i> B632 (DSM 24706) (1:1) (10^9 CFU) vs. Placebo daily at breakfast	3 months	Quality of life: None reported. Gastro Symptoms: None reported. Markers of active disease: None reported. Biochemical and microbial data: Metagenomic analysis; 6 phyla revealed after sequencing (5 Bacteria and 1 Archaea). <i>Firmicutes</i> , high in control group (60–70%) and 50–60% in probiotic group. <i>Bacteroidetes</i> 20–40% in CD group, 10–20% in control group. <i>Proteobacteria</i> and <i>Verrucomicrobia</i> high in the placebo group. Statistically, <i>Actinobacteria</i> was low in CD group but increased after probiotic intake. <i>Euryarchaeota</i> , the only <i>Archaea</i> was found predominately in the control group. Cardiovascular risk factors: None reported.

Table 3. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Primec et al., 2019 [38] Slovenia DBRCT	Probiotic: 20 Placebo: 19 HC: 14	Probiotic: Age 9.2 ± 4.4 years Male 20% Placebo: Age 10.5 ± 5.1 years Male 31% HC: Age 10.1 ± 6.0 years Male 36% Dx: biopsy On GFD from 6 months to 15 years. No additional diagnosis. Blood and faecal sample analysed; DNA extraction and sequencing with QIAamp DNA stool Mini Kit and molecular analyses; absolute quantification using Quantitative PCR.	<i>B. breve</i> 72 BR03 (DSM 16604) (2×10^9 CFU) and <i>B.</i> <i>breve</i> B632 (DSM 24706) (2×10^9 CFU) vs. Placebo Daily at breakfast	3 months; 3 months follow-up	Quality of life: None reported. Gastro Symptoms: None reported. Markers of active disease: None reported. Biochemical and microbial data: In the probiotic and placebo group, TNF- α had a similar level as the healthy children. In CD patients, TNF- α had positive correlation with <i>Verrucomicrobia</i> and negative one with <i>Parcubacteria</i> . There was a high statistical significance between TNF- α and unclassified <i>Bacteria</i> group and positive correlation with TNF- alpha and unclassified <i>Archaea</i> . In CD patients, <i>Proteobacteria</i> correlated positively with acetic and propionic acid ($p = 0.452$, $p = 0.004$ and $p = 0.331$, $p = 0.045$, respectively), which led to <i>Proteobacteria</i> and total SCFAs ($p = 0.380$. $p = 0.017$). <i>Euryarchaeota</i> phylum had a positive correlation ($p = 0.351$, $p = 0.029$) to acetic acid. In Healthy Children, TNF-alpha had a negative association with <i>Firmicutes</i> ($p = 0.660$, $p = 0.010$) and negative correlation to <i>Euryarchaeota</i> ($p = 0.654$, $p = 0.011$). Cardiovascular risk factors: None reported.

Table 3. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Harnett et al., 2016 [34] Australia DBRCT	Probiotics: 21 Placebo: 21	Probiotic: Age 47.1 ± 16.1 years M/F (3/18) Placebo: Age 47.5 ± 12.9 years M/F (4/17) Dx: biopsy On GFD for at least 12 months and with persistent symptoms GFD Adherence: the three-day diet diary Compliance was 95.2% No additional diagnosis. Duodenal biopsy, blood and faecal samples analysed; DNA and PCR analysis.	VSL #3 blend of probiotic bacteria vs. Placebo sachet orally with water/juice at breakfast and super	12-week treatment	Quality of life: Assessed with the CDQ. 2 participants on the placebo and 2 participants on probiotic reported mild bloating. Partial improvement due to GFD, 100% of participants. However, residual gastrointestinal symptoms (mild to moderate) and fatigue were reported by all. Gastro Symptoms: None reported. Markers of active disease: 1 probiotic and 1 placebo participant had persistent villous atrophy. Biochemical and microbial data: Descriptive statistics for the predominant bacteria showed that only <i>Streptomyces</i> spp. ($p = 0.058$) was different between the two groups at baseline and 12 weeks and <i>Mycoplasma</i> sp. ($p = 0.026$), 12 weeks only. <i>Bifidobacteria</i> ($p = 0.001$) reduced significantly, and <i>Escherichia coli</i> ($p = 0.005$) increased over time. Cardiovascular risk factors: None reported.
Francavilla et al., 2019 [39] Italy DBRCT	Probiotics: 54 Placebo: 55	Probiotic: Age 43.3 (18.8–62.2) years Male 11% Placebo: Age: 44.6 (19.3–63.4) years Male: 16% Dx: biopsy on GFD > 2 years Persistent symptoms [IBS Severity Score System >75] Duration of GFD: Probiotic, 6.8 (2.6–16.7) years Placebo, 7.4 (3.5–17.5) years Additional Diagnosis: IBS Faecal sample analysed; DNA extraction with FastDNA Spin kit for soil, RNA extraction with stool total RNA purification kit.	Mixture of: <i>Lactobacillus casei</i> LMG 101/37 P-17504 (5×10^9 CFU), <i>Lactobacillus</i> <i>plantarum</i> CECT 4528 (5×10^9 CFU), <i>Bifidobacterium</i> <i>animalis</i> subsp. lactis Bi1 LMG P-17502 (10×10^9 CFU), <i>Bifidobacterium breve</i> Bbr8 LMG P-17501 (10×10^9 CFU), <i>B. breve</i> BI10 LMG P-17500 (10×10^9 CFU) vs. Placebo sachet Daily	2-week run-in; 6-week treatment; 6-week follow-up	Quality of life: Irritable bowel syndrome quality of life scores was not different in both probiotic and placebo groups. Gastro Symptoms: GI symptoms reduced. Gastrointestinal symptom rating scale: Probiotic, 12.2 ± 5.5 and Placebo, 16.7 ± 6.7 , reduced significantly for both groups from baseline. At the end of follow up Probiotic, 10.1 ± 4.1 Placebo 9.6 ± 4.2 . Markers of active disease: TTG-IgA (IU/mL): Probiotic, 0.8 (0–1.2); Placebo, 0.5 (0.2–1) Biochemical and microbial data: Probiotics: significant increased levels of presumptive lactic acid bacteria (<i>Lactobacillus</i> , <i>Lactococcus</i> , and <i>Streptococcus</i>) <i>Bifidobacterium</i> spp. and <i>Staphylococcus</i> spp. Higher levels of <i>Bifidobacterium</i> spp. after 6 weeks. Placebo: No statistical differences found in cultivable microbes. No statistical differences found between both groups for total bacterial community richness. Cardiovascular risk factors: None reported.

Table 3. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Smecuol et al., 2020 [40] Argentina DBRCT	Probiotic: 7 Placebo: 5	Probiotic: Male 0% Placebo: Male 20% Age 53 (43–57) years Dx: biopsy On GFD for >2 years No additional diagnosis. Blood and faecal sample analysed; Faecal total DNA extracted and sequenced.	<i>B. infantis</i> NLS-SS (4×10^9 CFU) vs. Placebo Daily	One week run in 3 weeks treatment 2 weeks washout 3 weeks switched treatment	Quality of life: None reported. Gastro Symptoms: Two patients in the probiotic group had gluten indigestion. Markers of active disease: No significant changes in the coeliac symptom index when comparing probiotic and placebo groups. Biochemical and microbial data: Significant improvement in CD symptom in probiotic group compared to highly symptomatic placebo group, $p = 0.046$. No difference between both groups with positive and negative serology. No significant differences in both groups for gluten immunogenic peptide excretion. Probiotic group had decreased levels of <i>Ruminococcus</i> spp. and <i>Bifidobacterium adolescentis</i> . Cardiovascular risk factors: None reported.
Ali et al., 2022 [41] Pakistan Randomized clinical trial, descriptive cross-sectional study.	Probiotic: 85 No medication: 85	Age 8–10 years Dx: CD from intestinal biopsy. No additional diagnosis. Stool frequency analysed.	<i>Clostridium butyricum</i> and <i>Bifidobacterium</i> spp. in 75–100 mL of boiled water twice daily.	28 days	Quality of life: None reported. Gastro Symptoms: Significant reduction in frequency of stools per day. Markers of active disease: None reported. Biochemical and microbial data: None reported. Cardiovascular risk factors: None reported.

CD: Coeliac Disease, DBRCT: Double Blind Randomized Controlled Trial, GFD: Gluten-free Diet, M/F: Male/Female, HC: Healthy Control, Dx: Diagnosis, F/u: Follow-up, IBS: Irritable bowel syndrome.

Table 4. Characteristics of studies and reported outcomes for non-RCTs.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Pinto-Sanchez et al., 2016 [36] Argentina	Active CD with probiotic: 12 Active CD without probiotic: 24. Control CD on 1 y GFD: 5	CD Active on probiotics: Age 41 (22–53) years Female n (%): 8 (67) CD Active no treatment: Age 40 (29–54) years Female n (%): 23 (95.8) CD on GFD: Age 35 (31–45) years Female n (%): 4 (80) Dx: biopsy Active cases No additional diagnosis. Duodenal biopsy analysed.	<i>Bifidobacterium infantis</i> NSL-SS	3 weeks	Quality of life: None reported. Gastro Symptoms: None reported. Markers of active disease: None reported. Biochemical and microbial data: The probiotic reduced the Paneth cells (PC) counts without the GFD. However, decreased macrophage counts ($p = 0.02$) were seen after 1 y GFD as well as further decreased in patients treated with the probiotic only. Similarly, the expression of mucosal HD-5 was significantly decreased in the probiotic group but not in 1 y GFD ($p < 0.001$). IgA TG: Active CD without probiotic 129 (104–200), Active CD with probiotic 200 (192–216), CD on 1 y GFD 8 (4–17) IgA DGP: Active CD without probiotic 200 (120–300), Active CD with probiotic 152 (64–300), CD on 1 y GFD 7 (4–18) Cardiovascular risk factors: None reported.

Table 4. Cont.

Author Year Country Study Design	Sample Size	Population Characteristics	Interventions (Probiotic and Placebo)	Follow Up Duration	Outcomes
Martinello et al., 2017 [37] Brazil Non- randomized clinical trial	CD: 14 HC: 17	CD: Age 18–60 years 10/4 (F/M) HC: Age 18–85 years years 10/7 (F/M) Dx: biopsy On GFD and asymptomatic No additional diagnosis. Faecal sample analysed; for bifidobacteria content and faecal pH.	10 ⁸ CFU of <i>Lactobacillus</i> <i>acidophilus</i> and <i>Bifidobacterium lactis</i> as 100 g of yogurt per day. the average concentration of bifidobacteria was 6.67 × 10 ⁸ ± 10.3 × 10 ⁸ CFU/g of yoghurt.	30 days	Quality of life: None reported. Gastro Symptoms: None reported. Markers of active disease: None reported. Biochemical and microbial data: Healthy individuals presented a significantly higher concentration of bifidobacteria (2.3 × 10 ⁸ ± 6.3 × 10 ⁷ CFU/g) before the probiotic-containing yogurt intake when compared to the celiac group (1.0 × 10 ⁷ ± 1.7 × 10 ⁷ CFU/g) Celiac patients presented, in average, 83% less bifidobacteria than healthy individuals. Still, celiac faecal pH (7.19 ± 0.521) was not significantly different from the faecal pH of the control group (7.18 ± 0.522). Healthy individuals presented a significantly higher bifidobacteria concentration (14.7 × 10 ⁸ ± 0.2 × 10 ⁸ CFU/g) than celiac patients (0.76 × 10 ⁸ ± 0.1 × 10 ⁸ CFU/g). However, faecal pH of celiac patients (7.28 ± 0.518) did not show significant difference from the faecal pH of healthy individuals (7.07 ± 0.570) after the yogurt intake. Cardiovascular risk factors: None reported.

CD: Coeliac Disease, GFD: Gluten-free Diet, M/F: Male/Female, HC: Healthy Control, Dx: Diagnosis, F/u: Follow-up.

The Effect of Probiotics on GI Symptoms: Five studies assessed the impact of probiotics on GI symptoms (Tables 3 and 4). Four studies reported improvements in GI symptoms after comparing probiotic to placebo [27,28,35,37]. Smecuol et al. reported improvements in bloating, diarrhoea, abdominal pains, and abdominal distension from self-reported records [27]. Olivares et al. also reported improvements in abdominal pains, vomiting, constipation and diarrhoea from self-reported records [28]. Ali et al. reported significant improvements in stool frequency [37], though the study had a high risk of bias (Table 1). Francavilla et al. reported no difference in diarrhoea when using the Bristol Stool Form Scale and was considered a low risk of bias (Table 2) [35]. Smecuol et al. and Francavilla et al. [27,35] used gastrointestinal symptom rating scale (GSRS) questionnaires and reported a significant reduction in GSRS scores compared with baseline values. Smecuol et al. [36] used the coeliac symptoms index (CSI) while Harnett et al. [30] used CDQ-GI to assess GI symptoms of participants. Probiotics when compared to placebo did not show significant changes in CSI scores.

3. Discussion

Data on the effect of probiotics in coeliac disease related gastrointestinal symptoms are limited, and data on CVD risks is even less studied. CVD is associated with a chronic state of low-grade inflammation, whereby the microbiota has an impact on maintaining the gut barrier function, critical for reducing the amount of pro-inflammatory bacterial byproducts that can cross into the bloodstream [8]. Notably, the two studies that evaluated the effects of probiotics on serum TNF- α reported a reduction in levels [28,29], agrees with a meta-analysis of 12 RCTs in people with diabetes or prediabetes [8]. Naseri et al. suggests the modulating effects of probiotics on TNF- α levels (and CRP levels) were more pronounced in patients with heightened inflammation [8]. The two studies included European children with CD only, thus, it is clear further studies exploring the impact of probiotics on cardiovascular risk and inflammation are needed. Smecuol et al. [27] reported that a probiotic intervention had no significant impact on intestinal permeability, however, the intervention was only 3 weeks, and it is well known that it may take some time before mucosal integrity returns to baseline [38]. Patients with CD continue to have gluten exposures which may account for persistence of histologic inflammation and residual symptoms. If patients are able to completely exclude all gluten, then it remains debated whether the inflammation remains [39].

Four studies reported improvements in GI symptoms after comparing probiotic to placebo [27,28,35,37], although there was a high risk of bias in the outcome measurement for Ali et al., study. Since completing the systematic literature search, Khorzoghi et al. reported improved fatigue scores with probiotic supplementation in a small cohort of adults with CD from Iran [40]. A meta-analysis by Seiler et al. [25] concluded probiotics may improve gastrointestinal symptoms, however, the quality of evidence was low or very low; we confirm the recent publications have not been able to overcome this criticism.

A strength of our systematic review is collating all reported outcomes from RCTs and non RCTs relating to the impact of probiotic supplementation in adults and children with coeliac disease. We also bring attention to the reader that three publications were from the same intervention study in Slovenia [29,31,34], thus the body of evidence for probiotics in CD is small. This systematic review was conducted rigorously with pre-defined outcomes and a pre-registered protocol. We highlight that only two studies reported how they determined adherence to a GFD, it is well recognised that adhering to the gluten-free diet is challenging and many patients do not achieve full adherence [4]. We recommend all future studies investigating probiotics in CD include an assessment for dietary adherence to the GFD as consumption of gluten would have a substantial impact on study outcomes such as intestinal permeability and inflammatory markers.

Four studies reported the composition of the microbiota with an increase in bifidobacterial evident after the probiotic interventions as would be expected, Mozafarybazargany et al. [26] reported similar findings from pooled analysis from a broad range of studies including

people with CD and potential CD. The dysbiosis in treated CD maybe mainly food-induced, but in a small sample of children there is a demonstration of a constant alteration of some species that clustered in CD and not in healthy controls [41]. The gut microbiota differs from person to person geographically; thus, the effectiveness of a probiotic may vary for persons in specific geographic areas [42]. The review comprised of studies conducted in Europe (Italy, Spain and Slovenia), Australia, South America (Brazil and Argentina) and South Asia (Pakistan) with none from Africa, East Asia and North America; therefore, the results cannot be easily generalized. Knowing the impact of probiotics on the microbial ecosystem is essential; however, it must be emphasized that not all probiotics contain the same bacterial strains and can have different beneficial effects.

To conclude, our systematic review reveals there remains very sparse data on outcomes related to cardiovascular risk, and presently our knowledge of the area relies on data from other disease-based populations. There is emerging evidence of an impact on inflammation and gastrointestinal symptoms in adults and children with CD.

4. Methods

The systematic review was undertaken and reported in line with the guidelines of preferred reporting items for systematic reviews and meta-analyses [43]. A population, intervention, comparison and outcomes (PICO) framework and literature search strategy criteria were developed—including the PICO table. This review has been registered on Prospero, the international prospective register of systematic reviews (CRD42023380433)

4.1. Inclusion and Exclusion

We adapted the PICO table strategy for the inclusion and exclusion criteria. Participants/persons, i.e., children and adults diagnosed with coeliac disease using standard procedures including specific serologic tests (anti-tissue transglutaminase, anti-deamidated gliadin peptide, or anti-endomysia antibodies) and confirmed by duodenal biopsy (Marsh score 3 or higher; or equivalent). Interventions included (any dietary intervention using probiotics with a duration of at least 21 days. For comparison, dietary interventions compared to placebo, or any or any other therapy were considered.

Outcomes assessed were all reported outcomes, this included quality of life, gastro symptoms, biochemical and microbial data, inflammatory markers and any cardiovascular risk factors. Assessment of stool frequency, stool consistency, bloating, flatulence, abdominal pain prior during and after the dietary intervention. Markers of active disease (total immunological immunoglobulin A (IgA) and IgA tissue transglutaminase; IgA endomysial antibodies (EMA), IgG deamidated gliadin peptide (DGP) or IgG tTG). Studies that did not meet the criteria were excluded.

4.2. Type of Studies

The systematic review included randomized controlled trials, experimental studies, and non-controlled trials, which were human trials only in this study. There were no restrictions on study size. Observational studies, case reports, and case series were excluded. Duplicate studies and studies without validated diagnoses of CD were also excluded. We conducted a comprehensive search in the following databases: CINAHL, Web of Science, CENTRAL, PubMed, Australian and New Zealand Clinical Trials Register and ClinicalTrials.gov from inception up to March 2023.

4.3. Search Terms

The search strategy was based on Medical Subject Headings (MeSH) and other corresponding words. The terms include “Probiotics”, “*Bifidobacterium*”, “*Lactobacillus*”, “Coeliac Disease”, “Celiac disease”. We used the logical operators “OR” or “AND” to connect the terms above. The search syntax: “Coeliac disease” OR “Celiac disease” AND probiotics OR “probiotic supplementation” was used on CINAHL, CENTRAL and Web of Science Core Selection. The syntax: (“Celiac Disease” [MeSH Terms] OR “Celiac Disease” [Text

Word] OR “Coeliac Disease” [Title/Abstract] OR “CD” [All Fields]) AND (“Probiotics” [MeSH Terms] OR “probiotic*” [Text Word] OR “probiotic supplement” [Title/Abstract] OR “Probiotic supplementation” [Title/Abstract]) was used on PubMed Search. The total search results from PubMed Search were 665 results, Web of Science had 6264 results, CENTRAL produced 67 results and CINAHL, 2676 results.

4.4. Selection of Studies

Two independent authors (LF and CS), screened titles and abstracts and cleared duplicates as well. Full-text screening was performed by the same reviewers independently. All data were collated in the AI software tool Rayyan and after screening, selected articles were collected into a Rayyan file. For any disagreement case, with the help of an independent third author (YJ), a resolution was reached.

Two independent reviewers (LF and YJ) extracted data and information on authors, publication type (abstract/full text), publication year, geographic region (country), language, follow-up duration, age, gender, ethnicity, method of diagnosis (biopsy/serology/HLA DQ2/8 status), adherence to a gluten-free diet, additional diagnosis such as IBS, Probiotic strain/combination and type of delivery, dosage, frequency (timing), duration of intervention (length). Comparator population characteristics and dosage, frequency, duration of intervention placebo type, GI symptom scores, QOL scores, adverse events, markers of active disease such as serum TNF- α , intestinal permeability.

4.5. Data Synthesis Strategy

Our data synthesis was conducted based on data availability and it comprised studies grouped under all reported outcomes and study details (e.g., number of participants, setting, etc.). Individual study data including specific study outcomes, methods of analysis and results were reported in tables. A narrative synthesis was then carried out by tabulation and narrative summary of populations, interventions, and outcomes. Meta-analysis was not undertaken due to the large heterogeneity between the studies.

4.6. Risk of Bias Assessment

Selected articles were reviewed for risk of bias using Cochrane risk of bias in RCTs (ROB-2 tool) and non RCTs (ROBINS-1 tool) [44,45]. The Cochrane risk of bias assessment tools were used to assess randomization; concealment and blinding of participants, outcome assessors; deviations from intended interventions, missing outcome data, measurement of outcomes and selection of reported results. The first reviewer independently (LF) assessed the quality of selected articles for all domains of the tool so did a second reviewer (YJ). A table summarising the findings was created to display the quality of each study.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/gidisord6010008/s1>.

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