BMJ Nutrition, Prevention & Health

Coeliac disease and microbiota: is it time for personalised biotics intervention? A scoping review

Francesco Valitutti ,[1,2] Elena Cavalli,[3] Beatrice Leter,[4] Maureen Leonard,[5] Fasano Alessio,[5] Salvatore Cucchiara[5]

To cite: Valitutti F, Cavalli E, Leter B, *et al*. Coeliac disease and microbiota: is it time for personalised biotics intervention? A scoping review. *BMJ Nutrition, Prevention & Health* 2025;**0**. doi:10.1136/bmjnph-2024-001100

[1]Pediatrics Section, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[2]European Biomedical Institute of Salerno, Salerno, Italy
[3]Pediatric Unit, ASL Rieti, Rieti, Italy
[4]Department of Maternal Child Health, Sapienza University of Rome, Rome, Italy
[5]Center for Celiac Research and Treatment, Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to
Dr Francesco Valitutti;
francesco.valitutti@unipg.it

Received 2 November 2024
Accepted 11 March 2025

ABSTRACT

Rational A true increase in prevalence of coeliac disease (CeD) has been witnessed worldwide. This 'on-the-rise' epidemiological trend for CeD is shared with other immune-mediated disorders and could be due to environment-driven gut microbiota perturbances.

Objectives To summarise recent evidence regarding possible relationships between microbiota disturbances and CeD onset, with a specific focus on pathogenesis and possible biotic-based therapeutic interventions.

Methods A literature search was launched on 20 August 2024 using Google Scholar, PubMed, EMBASE, Scopus using keywords as follows: celiac disease AND microbiota; celiac disease AND microbiome; celiac disease AND prebiotics; celiac disease AND probiotics; celiac disease AND symbiotics; celiac disease AND postbiotics.

Results A total of 1779 articles were retrieved from two authors' blinded search, of which 1297 were duplicates. 206 articles were excluded by abstract as they were commentaries, letters, case series. A final set of 276 articles was suitable for the scope of our review and, after carefully reading the full-text articles, only 131 were considered valuable for the review and included as references for the review.

Conclusions While there is extensive literature on microbiota alterations and CeD, lack of clarity remains regarding whether the changes observed in the microbiota of individuals with CeD are effects of the condition or if and how they play a role in its onset. Limited evidence points towards the utility of specific probiotic strains to reduce symptoms, decrease inflammation, support growth in children and overall enhance recovery in CeD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the last decades, an increased prevalence for coeliac disease (CeD) has been witnessed, and this trend is shared with other immune-mediated disorders, suggesting underlying environment-driven gut microbiota perturbances.

WHAT THIS STUDY ADDS

⇒ This scoping review summarises up-to-date evidence regarding possible relationships between microbiota disturbances and CeD onset, with a specific focus on pathogenesis and possible biotic-based therapeutic interventions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While there is extensive literature on microbiota alterations and CeD, lack of clarity remains regarding whether the changes observed in the microbiota of individuals with CeD are causes or consequences of the condition. This knowledge gap calls for more data from ongoing prospective studies with multiomics approaches. Moreover, as regards possible biotic-based therapeutic interventions in CeD, a shift towards personalised compounds aiming to balance alterations induced by genetics and personal environmental exposures will be needed to truly intercept disease in its early stages or to complement the gluten-free diet for symptom control or enhanced mucosal recovery.

INTRODUCTION

Coeliac disease (CeD) is a systemic immune-mediated disease elicited by the ingestion of gluten and related prolamins in human leucocyte antigen (HLA)-DQ2 and HLA-DQ8 positive individuals who lose immunological tolerance towards those dietary peptides.[1]

Prevalence ranges between 1% and 2% in western countries and there is an increasing trend of diagnoses worldwide.[2]

Besides increased awareness and more frequent testing, there is also evidence that there is a true increase in prevalence which could be due to environment-driven gut microbiota perturbances.

The scope of this review is to summarise recent evidence regarding possible relationships between microbiota disturbances and CeD onset, with a specific focus on pathogenesis and possible biotic-based therapeutic interventions. A literature search was launched on 20 August 2024 using Google Scholar, PubMed, EMBASE, Scopus using keywords as follows: celiac disease AND microbiota; celiac disease AND microbiome; celiac disease AND prebiotics; celiac disease AND probiotics; celiac disease AND symbiotics; celiac disease AND postbiotics. A total

of 1779 articles were retrieved from 2 authors' blinded search, of which 1297 were duplicates. 206 articles were excluded by abstract as they were commentaries, letters, case series. A final set of 276 articles was suitable for the scope of our review and, after carefully reading the full-text articles, only 131 were considered valuable for the review and included as references for the review.

Microbiota's functions in human health

The human body harbours about 10–100 trillion microbial cells, and the microbial microbiome has a set of genes of approximately 3.3 million active genes compared with approximately 23 000 human genes.

Gut microbiota ideally establishes a symbiotic relationship with its host and plays an essential role in gut development and maturation.

Microbial composition and quantity vary along the gastrointestinal (GI) tract. Specifically, there is a gradual increase in number and species diversity from the duodenum to the colon, with a progressive increase in the proportion of Gram-positive to Gram-negative bacteria.[3]

The bacterial components of human gut microbiota consist of five major phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia.[4]

Although bacteria are the best-characterised component of the gut microbiota, other micro-organisms exert an important role such as viruses, fungi, parasites and archaea.[5–8]

Drivers of microbiota trajectories and CeD

Recent evidence underlined that gut microbiota development may start in utero,[9] and it matures in the first 2–3 years of life. It is primarily influenced by maternal diet and mode of delivery.

After the first few years of life, the microbiota becomes more stable and 'adult-like' in its composition.[10] Diversity and composition vary between individuals and within individuals over time, being strongly influenced by several environmental conditions such as diet, antibiotic exposure, among others.[11]

Genetics

The gut microbiota of CeD patients is influenced by genetic factors. A reduction of Bifidobacteria is seen also in breast-fed infants with a high genetic risk (HLA-DQ2).[12] Sellitto *et al* revealed that infants with high-risk genetics exhibited an increased prevalence of Firmicutes and Proteobacteria,[13] while another study found that taxa-related SNPs were linked to the Firmicutes and Proteobacteria phyla,[14] whose abundance has been shown to be altered in CeD patients.[15 16] However, the importance of the association between genetic factors, microbiota and CeD development was mitigated by the prospective ABIS study (All Babies In Southeast Sweden).[17] Although they identified core microbes correlated with the presence or absence of HLA haplotypes, the gut microbiota patterns in infants with subsequent development of CeD seemed to be more associated with external environmental factors rather than HLA.

Delivery mode

Caesarean section is associated with a decreased abundance of *Bacteroides vulgatus, Bacteroides dorei* and folate biosynthesis pathway along with an increased abundance of hydroxyphenylacetic acid metabolism in the infant. These patterns have been reported to be associated with impaired immune function[18] and inflammatory conditions such as type 1 diabetes mellitus and ulcerative colitis,[19] suggesting that they could also predispose infants to develop other autoimmune conditions. An Italian multicentre registry identified a higher rate of C-section births for CeD patients and showed that emergency C-section seems to be associated with an earlier onset of CeD compared with vaginal delivery or elective CS.[20] However, a recent review of available meta-analyses on non-genetic factors for CeD has shown no impact of delivery mode on disease risk.[21] It is more likely that it might work in concert with other perinatal factors leading to 'multiple-hit' microbiota perturbations.

Fetal and infant feeding

Maternal diet during pregnancy has been proposed to influence the risk of autoimmune diseases, including CeD. Although the The Environmental Determinants of Diabetes in the Young (TEDDY) study found no relationship between maternal consumption of gluten during late pregnancy and subsequent risk of CeD in the offspring,[22] a recent study demonstrated that higher fibre intake and lower gluten consumption during pregnancy were associated with a lower risk of CeD in the offspring.[23]

The relationship between breastfeeding and CeD is not clear, with contrasting data. Some studies analysed the possible association between breastfeeding and CeD, finding alterations of gut microbiota in children fed with formulas.[24 25] Few retrospective studies[26 27] have described a potential protective effect of breastfeeding on the development of CeD; however, other retrospective and prospective studies did not corroborate this protective effect.[28–36] This apparent discrepancy may be explained by the fact that breastfeeding per se may not be solely responsible for establishing a protective microbiota profile, being influenced by other lifestyle factors that may affect the clinical outcome if not properly analysed. Olivares *et al* demonstrated that *Clostridium perfringens* and *Clostridium difficile* are specifically associated with the formula feeding pattern.[24]

Vitamin D

The role of vitamin D in modulating the immune system is known. Its deficiency or insufficiency has been linked to an increased rate of autoimmune diseases, also through microbiota disruptions.[37] Although one study hypothesised a potential association between vitamin D and increased risk of CeD,[38] these data were not confirmed in other settings.[39 40]

Medications

Several studies have evaluated the potential association between antibiotics and CeD. Some found an increased risk of CeD after antibiotic exposure, in particular in the first years of life,[41–43] while others showed no association between CeD onset and antibiotic exposure.[44 45] Gut microbiota becomes more stable by 3 years of age[46] and antibiotic exposure during this crucial period of microbiota engraftment could alter immunological maturation.[47] Specifically, Mårild *et al* reported in a Swedish register-based study that antibiotic exposure up to 3 years before the diagnosis was associated with the risk of developing CeD at all ages.[48] Additionally, a cohort of more than 14 000 children demonstrated a significant antibiotic dose-dependent relationship for CeD and other chronic conditions, which was stronger in girls than in boys.[49]

The prospective Celiac Disease Genomic Environmental Microbiome and Metabolomic (CDGEMM) study showed that zonulin levels, a biomarker of gut permeability, increase in children who developed CeD months ahead of the onset of the disease but not in control subjects.[50] This study also showed that antibiotic exposure influenced zonulin levels in cases but not in controls, with the greater the number of antibiotic exposures, the greater the increase in zonulin before disease onset. Conversely, antibiotic exposure during prenatal life does not seem to be a potential risk factor for developing CeD.[51 52]

The relationship between the use of proton pump inhibitors (PPIs) and CeD pathogenesis also points towards possible microbiome interference.[53] Some studies found that the use of PPIs could exert an influence on the gut microbiome by modulating the inflammatory response in the mucosa and promoting the development of CeD in susceptible individuals.[54] This hypothesis is supported by the study of Freedberg *et al* which showed that high-dose PPI treatment significantly affected certain taxa and was associated with an increase in genes involved in bacterial invasion of epithelial cells.[55]

Altered microbiota and CeD immune activation

Several studies have demonstrated the possible association between alterations of gut microbiota and development of CeD. Broadly, some studies suggest an increase of Bacteroides, which exert a potential proinflammatory action, and a decrease of Bifidobacteria, which could have a protective role against inflammation.[56–63]

A recent study[64] showed that Bifidobacterium angulatum was significantly increased in duodenal mucosal samples of children with CeD. However, other studies[65–68] showed no significant differences in the gut composition of bacteria between CeD patients versus healthy controls. A recent study evaluated the gut microbiota of CeD children at diagnosis compared with healthy controls and demonstrated a dominance of Enterobacteriaceae and subdominance of Bacteroidetes/Streptococcus in duodenal samples of CeD patients, and a lower abundance of Bacteroides-Prevotella, Akkermansia and Staphylococcaceae in stool samples of CeD patients.[69] In addition, this study suggests proinflammatory microbiota imbalances are linked with CeD symptoms as patients with abdominal pain showed an increased number of Bacillaceae and Enterobacteriaceae, while patients with diarrhoea had reduced abundance of Clostridium cluster and Akkermansia and an increase in Bacillaceae and Fusobacterium.

Specific bacterial species/strains could have a pathogenetic role in the development of CeD. *Escherichia coli* clones isolated from CeD patients carry more virulent genes such as specific fimbriae and haemolysins than the species isolated from controls.[70] The increased prevalence of pathogenic bacteria could cause a proinflammatory environment that favours mucosal permeability and alters immune function. For example, using a mouse mode of CeD, *Bifidobacterium longum* CECT 7347 was found to decrease the synthesis of proinflammatory cytokines and histological damage,[71] as well as to ameliorate the immunogenicity of some gliadin peptides in mouse models.[72] A different strain of *B. longum*—NCC2705—was shown to produce a serine protease inhibitor and has immunomodulatory characteristics, that is, capable of attenuating the histological damage induced by gliadin in animal models of CeD such as DQ8-positive NOD mice.[73]

Information about gut microbiota composition in CeD is based on the analysis of duodenal or faecal samples. Studies based on faecal samples only are also limited by the fact that they provide qualitative and quantitative information that is not immediately comparable. Additionally, given the evolving fields of technologies used in the analysis during the last decades, the detection has been limited to the most represented bacteria, with very little information about their cooperation and their conjunct metabolic effect. Lastly, almost all of them are affected by small sample sizes which allow highly individual microbial profiles to greatly bias results and give rise to contradictory findings.

The CD-GEMM study was launched in 2014 to solve these controversies and to identify environmental factors leading to the loss of immune tolerance in CeD. Its analysis relies on shotgun metagenomic sequencing, allowing functional characterisation of the microbiota rather than plain taxonomic assignment available by 16S rRNA amplicon sequencing.[74]

In a recent study from this cohort, the CD-GEMM research team analysed the impact of both genetic and environmental risk factors on the development of the gut microbiota.[25]

Children at high genetic risk, born by C-section, with early exposure to antibiotics and formula-fed presented an increased abundance of Ruminococcus gnavus and Lachnospiraceae, showing that HLA genetics in combination with other early environmental exposures influence the microbiota towards inflammation in children at risk of CD even before food weaning. The trajectory of the microbiota composition in children at risk of CeD in the months preceding seroconversion and CeD diagnosis was also assessed in the CD-GEMM cohort[75]; in this substudy,

Table 1 List of available interventional studies on prebiotics, probiotics and postbiotics in coeliac disease

Authors	Composition/strains	Study design	Number of patients (paediatric or adult)	Treatment duration	Outcome/findings
Smecuol *et al*[120]	Bifidobacterium infantis natren life start strain super strain	Double-blinded placebo-controlled	22 adults, GCD	3 weeks	Symptom improvement, no change in intestinal permeability
Olivares *et al*[114]	*Bifidobacterium longum* CECT 7347	Double-blinded, placebo-controlled	33 children, GFD	3 months	Reduced numbers of Bacteroides fragilis group and the content of sIgA in stools—increased growth percentiles
Klemenak *et al*[113]	*Bifidobacterium breve* BR03 and *B. breve* B632	Double-blinded, placebo-controlled	49 children, GFD	3 months	Decreased production of proinflammatory cytokine TNF-α in children with CD on GFD.
Quagliariello *et al*[116]	*B. breve* strains (B632 and BR03)	Double-blinded, placebo-controlled	40 children, GFD	3 months	Increase *Actinobacteria,* re-establishment of the *Firmicutes/Bacteroidetes* ratio
Pinto-Sánchez *et al*[121]	Bifidobacterium infantis Natren Life Start super strain	Double-blinded placebo-controlled	41 adults, GCD (5 on GDF)	3 weeks	Reduced duodenal mucosa Paneth cell counts and expression of α-defensin-5
Feruś *et al*[125]	Oligofructose-enriched inulin (synergy 1) (prebiotic)	Double-blind placebo-controlled	34 children, GFD	3 months	Decrease in serum hepcidin concentration
Drabińska *et al*[127]	Oligofructose-enriched inulin (synergy 1) (prebiotic)	Double-blind placebo-controlled	34 children, GFD	3 months	Increase in Bifidobacterium count in the stool, increase in faecal acetate and butyrate levels Significant increase in serum 25-OH D and vitamin E
Håkansson *et al*[115]	*L. plantarum* HEAL9 paracasei 8700:2	Double-blinded, placebo-controlled	78 children, GCD	6 months	Reduced serum IgA-anti-transglutaminase, down regulatory effects on activated CD4+cells
Primec *et al*[117]	*B. breve* BR03 (DSM 16604) and *B. breve* B632 (DSM 24706)	Double-blinded, placebo-controlled	40 children, GFD	3 months	Modulated the production of serum TNF-α and stool SCFA
Francavilla *et al*[122]	5 strains of Lactobacilli and Bifidobacteria	Double-blind placebo-controlled	109 adults, GFD	6 weeks	Improved IBS-like symptoms and an increase in gut microbiota bifidobacteria
Freire *et al*[128]	Microbiota-derived bioproducts (postbiotic) (butyrate, lactate, and polysaccharide A)	Intestinal organoids from CD and non-CD patients	11 adults (5 non-CD, 6 CD)	N/A	Improved epithelial barrier (increasing tight junction expression) and reduced gliadin-induced cytokine expression, such IL-15 and IFNγ
Ali *et al*[118]	*Clostridium butyricum and Bifidobacterium*	Randomised, open study	170 children, GFD	28 days	Improvement in stool consistency and frequency
Conte *et al*[129]	Postbiotic Lactobacillus paracasei (LP) CBA L74 and patient-derived organoids	Intestinal organoids from CD and patients	6 Children (3 CD and 3 non-CD patients)	N/A	Induction of autophagy in Caco-2 cells and prevention of gliadin effect
Lionetti *et al*[119]	5 strains of Lactobacillus and Bifidobacterium	Double-blinded placebo-controlled	96 children, GFD	12 weeks	Faster increase in BMI
Ramedani *et al*, 2024[124]	*B. longum*, *L. acidophilus* and *L. plantarum*	Observational, open	Wheat dough was fermented with a probiotic mixture	6 hours	Reduced immunogenic properties of gluten
Nikoloudaki *et al*[123]	Lactobacilli and their cytoplasmic extracts, Bacillus sp. and bacterial protease	Double-blind placebo-controlled	Health volunteers on GCD	42 days	Much lower amounts of residual gluten in the stools

BMI, body mass index; GCD, gluten-containing diet; GFD, gluten-free diet.

specific bacterial strains and specific metabolic pathways were differentially identified in subjects progressing towards CeD onset from those who did not, such as a reduction of *Streptococcus thermophilus*, *Faecalibacterium prausnitzii*, *Clostridium clostridioforme* and an increase of *Dialister invisus*, Parabacteroides sp., Lachnospiraceae, tryptophan metabolism, and metabolites serine and threonine. In further work, using an organoid macrophage co-culture system together with a unique novel strain of *B. vulgatus* found only in at-risk children from the CDGEMM study who did not develop CeD (control subjects), this unique strain of *B. vulgatus* was able *to* mitigate gliadin-induced toxicity on the epithelium and immune activation secondary to an epigenetic reprogramming of the cell turnover, inflammation and barrier function pathways.[76]

A recent prospective cohort study from Sweden (ABIS) investigated the contributory role of gut microbiota and microbial metabolites in CeD onset, showing that CeD progressors have a distinct gut microbiota composition, that is, a significant decrease of Bacteroides, Prevotella and Holdemanella and an increase of Dialister.[77] The major targets of the mucosal immune response in CeD progressors are protective commensals such as Coprococcus, *Bifidobacterium bifidum* and Clostridium.[78] *B. bifidum* is specifically targeted by IgA in healthy children. It is known that these species have the ability to regulate immune response by inducing IgA response, indirectly suggesting a potential immunoregulatory interplay.[79 80]

Virome, viral infections and CeD onset

The virome is influenced by several environmental factors, such as the mode of delivery, breastfeeding and viral GI infections.[81] In particular, infections of adenovirus, enterovirus, rotavirus and reovirus in early life have been associated with an increased risk of CeD onset.[82–87]

TEDDY study is a prospective study that investigated the association between environmental exposure and the development of CeD in children with familial predisposition to type-1 diabetes mellitus and genetic HLA compatible for CeD onset.[88] The differential risk of infections at different ages suggested that there could be a time-window effect before and after 1 year of age. This is a vulnerable period because it is the time when breastfeeding is stopped and maternal-fetal transplacental IgG antibodies decrease, causing transient immunodeficiency. These data paralleled previous results from a Norwegian study finding that frequent enterovirus infections between one and 2 years of age were associated with higher risk of CeD.[83] In this Norwegian cohort, this risk was even higher if children received a high gluten intake, suggesting a cumulative effect of these environmental factors.

It could be speculated that enteroviruses may induce an interferon 1-mediated activation of the immune system as it is caused by reovirus,[85 89] with overactivation of tissue transglutaminase enzyme amplified by high gluten intake. However, the TEDDY study could not show any effect of these viruses on virome, probably due to the rapid clearance of viruses from the stools after the infections.

A recent study by El Mouzan *et al* examined the virome using metagenomic sequencing in mucosal and faecal samples from children with new-onset CeD and controls.[90] They found alterations of virome composition in both faecal and mucosal samples in cases compared with controls. However, only faecal samples showed a significant difference with an increase of human polyomavirus 2, Enterobacteria phage mEpX1 and Enterobacteria phage mEpX2 in children with CeD compared with controls; at the same time, they also found a decrease of Lactococcus phages ul36 and Streptococcus phage Abc2. A separate study on gut virome and CeD identified Human_endogenous _retrovirus_K virus as marker of specific CeD gut microbiome both on mucosal and faecal samples.[91] This virus has a potential role in the modulation of immune system, and it could be related to autoimmune disorders, including CeD.[92]

Fungal dysbiosis and CeD

Few studies have investigated the role of fungi in CeD pathogenesis. El Mouzan *et al* analysed mucosal and faecal samples through metagenomic sequences in a cohort of children with new-onset CeD.[93] In particular, children with CeD showed an increased abundance of Tricholomataceae, Saccharomycetaceae and Candida; conversely, they showed less abundance of *Pichiaceae*, *Pichia kudriavzevii* and *Pneumocystis jirovecii* compared with controls.

Saccharomyces cerevisiae has been shown to be increased in patients with CeD at diagnosis and reduced in patients with CeD on a gluten-free diet (GFD).[94 95]

Several studies suggest that *Candida albicans* may be related to CeD progression[96 97] because it could stimulate the formation of antibodies against tissue transglutaminase.[98]

Although fungal dysbiosis in children with CeD is described, the functional role of fungi and their influence on CeD still need to be clarified.

Probiotics, prebiotics and postbiotics in CeD management

Probiotics aim to reverse a condition of dysbiosis to eubiosis, thus modulating both the intestinal and systemic immunity.[99–101] Some probiotics seem beneficial since they release endopeptidases with the ability to degrade gluten peptides.[102 103]

Prebiotics are represented by insoluble dietary fibres (eg, inulin, fructo-oligosaccharides, galacto-oligosaccharides) which represent nutrients for beneficial commensal bacteria, especially Bifidobacteria.[104]

Postbiotics (also known as 'non-viable probiotics') are modernly defined as functional, biologically active molecules that are derived from the bacterial metabolism of food matrices, not requiring living bacterial cells for their action in the intestinal lumen. Among them are metabolites secreted by bacteria such as enzymes, cell wall fragments, short-chain fatty acids (SCFAs) but also exopolysaccharides. Several experimental data document

their pleiotropic properties such as immunomodulatory, antibacterial, anti-inflammatory and antioxidant activities.[105 106]

All available interventional studies on biotics in CeD have been summarised in table 1.

There is a wide documentation that numerous strains of Lactobacilli and Bifidobacteria with documented proteolytic/peptidolytic activity are crucial for gluten digestion.[107] Other benefits of probiotics in CeD patient derive from their ability to improve the epithelial barrier function, that is, by promoting production of metabolites such as SCFA that prevent intestinal oxidative stress and inflammation.[108 109] Moreover, several probiotics can antagonise the adherence of pathobionts to the epithelium.[110] Probiotics, mainly Bifidobacterium strains, have also been shown to downregulate mRNA expression of proinflammatory markers and promote anti-inflammatory cytokines.[111 112] However, in the future, other species might also be considered for clinical trials, as a specific strain of *B. vulgatus* has been recently witnessed to counteract the increased permeability in an organoid model of CeD.[76]

Clinical trials have been conducted in adult and paediatric patients with CeD aimed at studying the effects of probiotics on different outcomes: (1) the modulation of immunological variables or gut microbiota profiles underlying CeD; (2) improvement of symptoms and signs of altered GI function, despite a correctly performed GFD and (3) pattern of nutritional and growth recovery in patients starting a GFD.

The effects of two oral probiotic strains of Bifidobacteria on both proinflammatory (TNFα) and anti-inflammatory (IL-10) serum cytokines have been tested in children with CeD on GFD diet.[113] Remarkably, 3 months after starting the trial, only the group on probiotics showed a significant decrease in the TNFα levels.

Olivares *et al* conducted a double-blind randomised placebo study in children with new-onset CeD on GFD to evaluate the effect of administration of *B. longum* CECT 7347.[114] There was an increase in growth percentiles and a marked decrease in peripheral $CD3^+$ T lymphocytes and TNF-α concentration in children on probiotics compared with those who received placebo. Noticeably, *B. longum* ingestion led to a significant reduction of faecal Bacteroides fragilis species and of faecal IgA content.

In a randomised placebo-controlled study in children with compatible HLA genetics and positive serum autoantibodies for CeD, on a gluten-containing diet, the effect of two Lactobacillus strains was evaluated on peripheral immunity markers.[115] Interestingly, subjects on probiotics showed a reduction of the serum levels of IgA-anti-transglutaminase as well as down regulatory effects on activated CD4+cells.

Quagliariello *et al* evaluated the effect of two *Bifidobacterium breve* strains on the microbiota profile of CeD children on GFD, showing a reduction of the Firmicutes/Bacteroidetes ratio in treated CeD patients.[116]

In a double-blinded placebo-controlled trial, two strains of *B. breve* were able to modulate the production of TNF-α and SCFA, highlighting their anti-inflammatory effect.[117]

In a randomised open study, children with a recent CeD diagnosis on a GFD received a mixture of *Clostridium butyricum* plus Bifidobacterium: patients who received these strains showed an improvement in stool frequency and consistency.[118]

Recently, Lionetti *et al* have evaluated the usefulness of a probiotic mix (five strains of Lactobacilli and Bifidobacteria) in children with CeD starting a GFD, highlighting a faster and higher increase in body mass index-z score in the treatment arm.[119]

In a double-blinded placebo-controlled trial in adults with CeD still on gluten-containing diet, Bifidobacterium infantis NLS-SS strain given for 3 weeks promoted a symptomatic improvement, scored on a Gastrointestinal Symptom Rating Scale, but intestinal permeability was not modified.[120] The same strain was studied in patients with active CeD, both on GFD and on gluten-containing diet[121] while *B. infantis* NLS-SS reduced duodenal mucosa Paneth cell counts and expression of α-defensin-5 in CeD patients, only GFD was effective in decreasing duodenal mucosa macrophage count.

Francavilla *et al* showed the efficacy of a mixture of five strains of Lactobacilli and Bifidobacteria in a randomised placebo-controlled trial in adults with CeD and on a GFD for ≥2 years for controlling IBS-like symptoms/signs, although with no improvements in terms of quality of life.[122]

The potential ability of a probiotic mixture to metabolise and digest gluten-derived peptides has recently been studied in healthy volunteers. A placebo-controlled randomised trial on several strains such as Lactiplantibacillus plantarum DSM33363, Lactiplantibacillus plantarum DSM33364, Lacticaseibacillus paracasei DSM33373, Limosilactobacillus reuteri DSM33374, Bacillus megaterium DSM33300, Bacillus pumilus DSM33297 and Bacillus pumilus DSM33355 showed that gluten content in the stools was markedly lower in subjects on probiotics than in those on placebo.[123]

The attempt of some other probiotic strains (*B. longum*, *Lactobacillus acidophilus* and *Lactiplantibacillus plantarum*) to hydrolyse gluten into low molecular weight peptides has been recently witnessed.[124]

The number of studies on the effectiveness of prebiotics in modifying the microbiota of CeD patients as well as in influencing both digestive symptoms and variables related to nutritional status and growth, are very few compared with the reports on the use of probiotics.

Feruś *et al* evaluated the efficacy of a prebiotic product (oligofructose-enriched inulin), in addition to GFD, on iron homeostasis, demonstrating some theoretical benefits in CeD patients with iron-deprived anaemia.[125] This finding echoes previous data on animal models with anaemia showing the effectiveness of prebiotics in modulating the expression of proteins involved in iron absorption.[126]

In another randomised study, the same prebiotic led to an increased Bifidobacterium count and a better fat-soluble vitamins profile.[127]

The use of postbiotics in clinical practice is even more limited, especially in immune-mediated disorders, such as CeD or inflammatory bowel disease. However, some data on cellular or animal models are beginning to emerge. Freire *et al* evaluated on intestinal organoids, derived from duodenal biopsies of CeD and non-CeD patients, the effects of microbiota-derived bioproducts in modulating the epithelium's response to gliadin.[128] The authors analysed the effect of butyrate, lactate and polysaccharide A. Remarkably, microbiota-derived bioproducts increased and reduced gliadin-induced cytokine expression, such as IL-15 and IFNγ.

Conte *et al* used Caco-2 cells to study the effects of the postbiotic Lactobacillus paracasei (LP) CBA L74 on different immunoinflammatory pathways related to the CeD pathogenesis.[129] The Caco-2 cells were treated with a peptic-tryptic digest of gliadin (PTG) and P31-43, before and after pretreatment with the postbiotic LP. Both the P31-43 peptide and PTG were able to activate mTOR, a tyrosine kinase able to regulate cell proliferation and inhibit the autophagy pathway, but this activation was prevented when a pretreatment with these postbiotics was provided.[130]

Other postbiotic products have been evaluated on epithelial inflammation and barrier function. Martorell *et al* have studied the properties of a heat-treated (HT), non-viable, *B. longum* strain, CECT-7347, a strain known for its anti-inflammatory properties and its abilities to improve intestinal integrity.[131] The authors used the nematode Caenorhabditis elegans and HT-29 cell cultures as eukaryotic model systems. HT-CECT-7347 was protective against oxidative stress and showed noteworthy properties such as reduction of acute inflammatory responses, maintenance of the epithelial barrier integrity and inhibition of bacterial colonisation.

CONCLUSIONS

In conclusion, while there is extensive literature describing and investigating the microbiota and CeD, the central issue remains the lack of clarity regarding whether the changes observed in the microbiota of individuals with CeD are effects of the condition or if and how they play a role in its onset. Only long-term longitudinal data which track at-risk individuals from birth through the development of CeD autoimmunity and into the full manifestation of the disease can clarify this. Gathering extensive data from a prospective longitudinal cohort with samples before and after disease development, such as the ongoing CD-GEMM cohort, may help accommodate individual differences, thereby enabling the identification of specific links between microbial makeup and disease onset, and perhaps offering therapeutic targets for preventing CeD.

As regards biotic intervention in patients diagnosed with CeD on a GFD, limited evidence points towards the utility of strains to reduce symptoms, decrease inflammation, support growth in children and overall enhance recovery. However, small sample sizes of the conducted studies and few strains tested limit the generalisability of the findings. Given the individual differences in the intestinal microbiota, it is likely that personalised biotics that aim to balance alterations induced by genetics, personal environmental exposures (eg, antibiotic exposure, diet, built environment) and other factors will be needed to truly target and intercept disease.

Acknowledgements All the authors acknowledge the University of Perugia for the funding support covering the article processing fee.

Contributors FV and SC conceived the article. FV, SC, BL, EC, ML and FA drafted the different subchapters of the article. FV and SC reviewed and edited the final draft. All the authors approved the final version of the manuscript. FV is the guarantor of the article.

Funding The Article Processing Fee was covered by the University of Perugia. Grant no: NA.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed by Ruggiero Francavilla, University of Bari, Italy.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

ORCID iD

Francesco Valitutti http://orcid.org/0000-0002-1473-2240

REFERENCES

1 Stahl M, Koletzko S, Andrén Aronsson C, *et al*. Coeliac disease: what can we learn from prospective studies about disease risk? *Lancet Child Adolesc Health* 2024;8:63–74.
2 Gatti S, Rubio-Tapia A, Makharia G, *et al*. Patient and Community Health Global Burden in a World With More Celiac Disease. *Gastroenterology* 2024;167:23–33.
3 Kastl AJ, Terry NA, Wu GD, *et al*. The Structure and Function of the Human Small Intestinal Microbiota: Current Understanding and Future Directions. *Cell Mol Gastroenterol Hepatol* 2020;9:33–45.
4 Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009;9:313–23.
5 Gholamzad A, Khakpour N, Hashemi SMA, *et al*. Exploring the virome: An integral part of human health and disease. *Pathol Res Pract* 2024;260:155466.
6 Rodriguez KA, Gurung M, Talatala R, *et al*. The Role of Early Life Gut Mycobiome on Child Health. *Adv Nutr* 2024;15:100185.
7 Bogza A, King IL, Maurice CF. Worming into infancy: Exploring helminth-microbiome interactions in early life. *Cell Host Microbe* 2024;32:639–50.
8 Duller S, Moissl-Eichinger C. Archaea in the Human Microbiome and Potential Effects on Human Infectious Disease. *Emerg Infect Dis* 2024;30:1505–13.
9 Collado MC, Segata N. Initial exploration of in utero microbial colonization. *Nat Med* 2020;26:469–70.
10 Ku HJ, Kim YT, Lee JH. Microbiome Study of Initial Gut Microbiota from Newborn Infants to Children Reveals that Diet Determines Its Compositional Development. *J Microbiol Biotechnol* 2020;30:1067–71.

11 González A, Fullaondo A, Odriozola A. Impact of evolution on lifestyle in microbiome. *Adv Genet* 2024;111:149–98.
12 Palma GD, Capilla A, Nova E, *et al*. Influence of milk-feeding type and genetic risk of developing coeliac disease on intestinal microbiota of infants: the PROFICEL study. *PLoS One* 2012;7:e30791.
13 Sellitto M, Bai G, Serena G, *et al*. Proof of concept of microbiome-metabolome analysis and delayed gluten exposure on celiac disease autoimmunity in genetically at-risk infants. *PLoS One* 2012;7:e33387.
14 García-Santisteban I, Cilleros-Portet A, Moyua-Ormazabal E, *et al*. A Two-Sample Mendelian Randomization Analysis Investigates Associations Between Gut Microbiota and Celiac Disease. *Nutrients* 2020;12:1420.
15 Wacklin P, Kaukinen K, Tuovinen E, *et al*. The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. *Inflamm Bowel Dis* 2013;19:934–41.
16 Sánchez E, Donat E, Ribes-Koninckx C, *et al*. Duodenal-mucosal bacteria associated with celiac disease in children. *Appl Environ Microbiol* 2013;79:5472–9.
17 Milletich PL, Ahrens AP, Russell JT, *et al*. Gut microbiome markers in subgroups of HLA class II genotyped infants signal future celiac disease in the general population: ABIS study. *Front Cell Infect Microbiol* 2022;12:920735.
18 Yoshida N, Emoto T, Yamashita T, *et al*. Bacteroides vulgatus and Bacteroides dorei Reduce Gut Microbial Lipopolysaccharide Production and Inhibit Atherosclerosis. *Circulation* 2018;138:2486–98.
19 Bayer AL, Fraker CA. The Folate Cycle As a Cause of Natural Killer Cell Dysfunction and Viral Etiology in Type 1 Diabetes. *Front Endocrinol (Lausanne)* 2017;8:315.
20 Iorfida D, Valitutti F, Vestri A, *et al*. Prevalence of delivery mode in an Italian nationwide cohort with celiac disease: a SIGENP multicenter retrospective study (the CD-deliver-IT). *Ital J Pediatr* 2024;50:129.
21 Tsali L, Evangelou E, Ntzani E, *et al*. Elucidating the non-genetic risk factors for celiac disease: an umbrella review of meta-analyses. *Eur J Gastroenterol Hepatol* 2024;36:1171–9.
22 Uusitalo U, Lee H-S, Aronsson CA, *et al*. Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort. *Am J Clin Nutr* 2015;102:1216–21.
23 Lund-Blix NA, Tapia G, Mårild K, *et al*. Maternal fibre and gluten intake during pregnancy and risk of childhood celiac disease: the MoBa study. *Sci Rep* 2020;10:16439.
24 Olivares M, Benítez-Páez A, de Palma G, *et al*. Increased prevalence of pathogenic bacteria in the gut microbiota of infants at risk of developing celiac disease: The PROFICEL study. *Gut Microbes* 2018;9:551–8.
25 Leonard MM, Karathia H, Pujolassos M, *et al*. Multi-omics analysis reveals the influence of genetic and environmental risk factors on developing gut microbiota in infants at risk of celiac disease. *Microbiome* 2020;8:130.
26 Ivarsson A, Hernell O, Stenlund H, *et al*. Breast-feeding protects against celiac disease. *Am J Clin Nutr* 2002;75:914–21.
27 Fälth-Magnusson K, Franzén L, Jansson G, *et al*. Infant feeding history shows distinct differences between Swedish celiac and reference children. *Pediatr Allergy Immunol* 1996;7:1–5.
28 Lionetti E, Castellaneta S, Francavilla R, *et al*. Introduction of gluten, HLA status, and the risk of celiac disease in children. *N Engl J Med* 2014;371:1295–303.
29 Norris JM, Barriga K, Hoffenberg EJ, *et al*. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA* 2005;293:2343–51.
30 Størdal K, White RA, Eggesbø M. Early feeding and risk of celiac disease in a prospective birth cohort. *Pediatrics* 2013;132:e1202–9.
31 Welander A, Tjernberg AR, Montgomery SM, *et al*. Infectious disease and risk of later celiac disease in childhood. *Pediatrics* 2010;125:e530–6.
32 Vriezinga SL, Auricchio R, Bravi E, *et al*. Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 2014;371:1304–15.
33 Ziegler AG, Schmid S, Huber D, *et al*. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003;290:1721–8.
34 Aronsson CA, Lee H-S, Liu E, *et al*. Age at gluten introduction and risk of celiac disease. *Pediatrics* 2015;135:239–45.
35 Decker E, Engelmann G, Findeisen A, *et al*. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. *Pediatrics* 2010;125:e1433–40.
36 Roberts SE, Williams JG, Meddings D, *et al*. Perinatal risk factors and coeliac disease in children and young adults: a record linkage study. *Aliment Pharmacol Ther* 2009;29:222–31.
37 Wu Z, Liu D, Deng F. The Role of Vitamin D in Immune System and Inflammatory Bowel Disease. *J Inflamm Res* 2022;15:3167–85.
38 Lebwohl B, Green PHR, Murray JA, *et al*. Season of birth in a nationwide cohort of coeliac disease patients. *Arch Dis Child* 2013;98:48–51.
39 Gorini F, Tonacci A. Vitamin D: An Essential Nutrient in the Dual Relationship between Autoimmune Thyroid Diseases and Celiac Disease-A Comprehensive Review. *Nutrients* 2024;16:1762.
40 Mårild K, Tapia G, Haugen M, *et al*. Maternal and neonatal vitamin D status, genotype and childhood celiac disease. *PLoS ONE* 2017;12:e0179080.
41 Canova C, Zabeo V, Pitter G, *et al*. Association of maternal education, early infections, and antibiotic use with celiac disease: a population-based birth cohort study in northeastern Italy. *Am J Epidemiol* 2014;180:76–85.
42 Dydensborg Sander S, Nybo Andersen AM, Murray JA, *et al*. Association Between Antibiotics in the First Year of Life and Celiac Disease. *Gastroenterology* 2019;156:2217–29.
43 Bittker SS, Bell KR. Potential risk factors for celiac disease in childhood: a case-control epidemiological survey. *Clin Exp Gastroenterol* 2019;12:303–19.
44 Myléus A, Hernell O, Gothefors L, *et al*. Early infections are associated with increased risk for celiac disease: an incident case-referent study. *BMC Pediatr* 2012;12:194.
45 Kemppainen KM, Lynch KF, Liu E, *et al*. Factors That Increase Risk of Celiac Disease Autoimmunity After a Gastrointestinal Infection in Early Life. *Clin Gastroenterol Hepatol* 2017;15:694–702.
46 Yatsunenko T, Rey FE, Manary MJ, *et al*. Human gut microbiome viewed across age and geography. *Nature New Biol* 2012;486:222–7.
47 Fenneman AC, Weidner M, Chen LA, *et al*. Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the gastrointestinal tract. *Nat Rev Gastroenterol Hepatol* 2023;20:81–100.
48 Mårild K, Ye W, Lebwohl B, *et al*. Antibiotic exposure and the development of coeliac disease: a nationwide case-control study. *BMC Gastroenterol* 2013;13:109.
49 Aversa Z, Atkinson EJ, Schafer MJ, *et al*. Association of Infant Antibiotic Exposure With Childhood Health Outcomes. *Mayo Clin Proc* 2021;96:66–77.
50 DaFonte TM, Valitutti F, Kenyon V, *et al*. Zonulin as a Biomarker for the Development of Celiac Disease. *Pediatrics* 2024;153:e2023063050.
51 Mårild K, Ludvigsson J, Sanz Y, *et al*. Antibiotic exposure in pregnancy and risk of coeliac disease in offspring: a cohort study. *BMC Gastroenterol* 2014;14:75.
52 Mårild K, Kahrs CR, Tapia G, *et al*. Maternal Infections, Antibiotics, and Paracetamol in Pregnancy and Offspring Celiac Disease: A Cohort Study. *J Pediatr Gastroenterol Nutr* 2017;64:730–6.
53 Jang S, Lebwohl B, Abrams JA, *et al*. Celiac disease serology and gut microbiome following protein pump inhibitor treatment. *Medicine (Baltimore)* 2020;99:e21488.
54 Lebwohl B, Spechler SJ, Wang TC, *et al*. Use of proton pump inhibitors and subsequent risk of celiac disease. *Dig Liver Dis* 2014;46:36–40.
55 Freedberg DE, Toussaint NC, Chen SP, *et al*. Proton Pump Inhibitors Alter Specific Taxa in the Human Gastrointestinal Microbiome: A Crossover Trial. *Gastroenterology* 2015;149:883–5.
56 Nadal I, Donant E, Ribes-Koninckx C, *et al*. Imbalance in the composition of the duodenal microbiota of children with coeliac disease. *J Med Microbiol* 2007;56:1669–74.
57 Collado MC, Donat E, Ribes-Koninckx C, *et al*. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *J Clin Pathol* 2009;62:264–9.
58 De Palma G, Capilla A, Nadal I, *et al*. Interplay between human leukocyte antigen genes and the microbial colonization process of the newborn intestine. *Curr Issues Mol Biol* 2010;12:1–10.
59 Di Cagno R, Rizzello CG, Gagliardi F, *et al*. Different fecal microbiotas and volatile organic compounds in treated and untreated children with celiac disease. *Appl Environ Microbiol* 2009;75:3963–71.
60 Sánchez E, De Palma G, Capilla A, *et al*. Influence of environmental and genetic factors linked to celiac disease risk on infant gut colonization by Bacteroides species. *Appl Environ Microbiol* 2011;77:5316–23.
61 Schippa S, Iebba V, Barbato M, *et al*. A distinctive "microbial signature" in celiac pediatric patients. *BMC Microbiol* 2010;10:175.

62 Sanz Y, Sánchez E, Marzotto M, *et al*. Differences in faecal bacterial communities in coeliac and healthy children as detected by PCR and denaturing gradient gel electrophoresis. *FEMS Immunol Med Microbiol* 2007;51:562–8.
63 Olivares M, Neef A, Castillejo G, *et al*. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. *Gut* 2015;64:406–17.
64 El Mouzan M, Al-Hussaini A, Serena G, *et al*. Microbiota profile of new-onset celiac disease in children in Saudi Arabia. *Gut Pathog* 2022;14:37.
65 Kalliomäki M, Satokari R, Lähteenoja H, *et al*. Expression of microbiota, Toll-like receptors, and their regulators in the small intestinal mucosa in celiac disease. *J Pediatr Gastroenterol Nutr* 2012;54:727–32.
66 Cheng J, Kalliomäki M, Heilig HGHJ, *et al*. Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease. *BMC Gastroenterol* 2013;13:113.
67 de Meij TGJ, Budding AE, Grasman ME, *et al*. Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease. *Scand J Gastroenterol* 2013;48:530–6.
68 Nistal E, Caminero A, Herrán AR, *et al*. Study of duodenal bacterial communities by 16S rRNA gene analysis in adults with active celiac disease *vs* non-celiac disease controls . *J Appl Microbiol* 2016;120:1691–700.
69 Di Biase AR, Marasco G, Ravaioli F, *et al*. Gut microbiota signatures and clinical manifestations in celiac disease children at onset: a pilot study. *J of Gastro and Hepatol* 2021;36:446–54.
70 Sánchez E, Nadal I, Donat E, *et al*. Reduced diversity and increased virulence-gene carriage in intestinal enterobacteria of coeliac children. *BMC Gastroenterol* 2008;8:50.
71 Laparra JM, Olivares M, Gallina O, *et al*. Bifidobacterium longum CECT 7347 modulates immune responses in a gliadin-induced enteropathy animal model. *PLoS One* 2012;7:e30744.
72 Laparra JM, Olivares M, Sanz Y. Oral administration of Bifidobacterium longum CECT 7347 ameliorates gliadin-induced alterations in liver iron mobilisation. *Br J Nutr* 2013;110:1828–36.
73 McCarville JL, Dong J, Caminero A, *et al*. A Commensal Bifidobacterium longum Strain Prevents Gluten-Related Immunopathology in Mice through Expression of a Serine Protease Inhibitor. *Appl Environ Microbiol* 2017;83:e01323-17.
74 Leonard MM, Kenyon V, Valitutti F, *et al*. Cohort profile: Celiac disease genomic, environmental, microbiome and metabolome study; a prospective longitudinal birth cohort study of children at-risk for celiac disease. *PLoS One* 2023;18:e0282739.
75 Leonard MM, Valitutti F, Karathia H, *et al*. Microbiome signatures of progression toward celiac disease onset in at-risk children in a longitudinal prospective cohort study. *Proc Natl Acad Sci U S A* 2021;118:e2020322118.
76 Tran T, Senger S, Baldassarre M, *et al*. Novel Bacteroides Vulgatus strain protects against gluten-induced break of human celiac gut epithelial homeostasis: a pre-clinical proof-of-concept study. *Pediatr Res* 2024;95:1254–64.
77 Girdhar K, Dogru YD, Huang Q, *et al*. Dynamics of the gut microbiome, IgA response, and plasma metabolome in the development of pediatric celiac disease. *Microbiome* 2023;11:9.
78 Deleu S, Machiels K, Raes J, *et al*. Short chain fatty acids and its producing organisms: An overlooked therapy for IBD? *EBioMedicine* 2021;66:103293.
79 Park JH, Um JI, Lee BJ, *et al*. Encapsulated Bifidobacterium bifidum potentiates intestinal IgA production. *Cell Immunol* 2002;219:22–7.
80 Konieczna P, Groeger D, Ziegler M, *et al*. Bifidobacterium infantis 35624 administration induces Foxp3 T regulatory cells in human peripheral blood: potential role for myeloid and plasmacytoid dendritic cells. *Gut* 2012;61:354–66.
81 Fulci V, Stronati L, Cucchiara S, *et al*. Emerging Roles of Gut Virome in Pediatric Diseases. *Int J Mol Sci* 2021;22:4127.
82 Kagnoff MF, Paterson YJ, Kumar PJ, *et al*. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut* 1987;28:995–1001.
83 Kahrs CR, Chuda K, Tapia G, *et al*. Enterovirus as trigger of coeliac disease: nested case-control study within prospective birth cohort. *BMJ* 2019;364:l231.
84 Dolcino M, Zanoni G, Bason C, *et al*. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunol Res* 2013;56:465–76.
85 Bouziat R, Hinterleitner R, Brown JJ, *et al*. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* 2017;356:44–50.
86 Stene LC, Honeyman MC, Hoffenberg EJ, *et al*. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am J Gastroenterol* 2006;101:2333–40.
87 Hemming-Harlo M, Lähdeaho ML, Mäki M, *et al*. Rotavirus Vaccination Does Not Increase Type 1 Diabetes and May Decrease Celiac Disease in Children and Adolescents. *Pediatr Infect Dis J* 2019;38:539–41.
88 Lindfors K, Lin J, Lee H-S, *et al*. Metagenomics of the faecal virome indicate a cumulative effect of enterovirus and gluten amount on the risk of coeliac disease autoimmunity in genetically at risk children: the TEDDY study. *Gut* 2020;69:1416–22.
89 Brown JJ, Jabri B, Dermody TS. A viral trigger for celiac disease. *PLoS Pathog* 2018;14:e1007181.
90 El Mouzan M, Assiri A, Al Sarkhy A, *et al*. Viral dysbiosis in children with new-onset celiac disease. *PLoS ONE* 2022;17:e0262108.
91 El Mouzan M, Assiri A, Al Sarkhy A. Gut microbiota predicts the diagnosis of celiac disease in Saudi children. *World J Gastroenterol* 2023;29:1994–2000.
92 Grandi N, Tramontano E. Human Endogenous Retroviruses Are Ancient Acquired Elements Still Shaping Innate Immune Responses. *Front Immunol* 2018;9:2039.
93 El Mouzan M, Al-Hussaini A, Fanelli B, *et al*. Fungal Dysbiosis in Children with Celiac Disease. *Dig Dis Sci* 2022;67:216–23.
94 Granito A, Zauli D, Muratori P, *et al*. Anti-Saccharomyces cerevisiae and perinuclear anti-neutrophil cytoplasmic antibodies in coeliac disease before and after gluten-free diet. *Aliment Pharmacol Ther* 2005;21:881–7.
95 Mallant-Hent RCh, Mary B, von Blomberg E, *et al*. Disappearance of anti-Saccharomyces cerevisiae antibodies in coeliac disease during a gluten-free diet. *Eur J Gastroenterol Hepatol* 2006;18:75–8.
96 Corouge M, Loridant S, Fradin C, *et al*. Humoral immunity links Candida albicans infection and celiac disease. *PLoS One* 2015;10:e0121776.
97 Aaron L, Torsten M. Candida albicans in celiac disease: A wolf in sheep's clothing. *Autoimmun Rev* 2020;19:102621.
98 Nieuwenhuizen WF, Pieters RHH, Knippels LMJ, *et al*. Is Candida albicans a trigger in the onset of coeliac disease? *Lancet* 2003;361:2152–4.
99 Chandrasekaran P, Weiskirchen S, Weiskirchen R. Effects of Probiotics on Gut Microbiota: An Overview. *Int J Mol Sci* 2024;25:6022.
100 Matera M, Guandalini S. How the Microbiota May Affect Celiac Disease and What We Can Do. *Nutrients* 2024;16:1882.
101 Bock PM, Martins AF, Schaan BD. Understanding how pre- and probiotics affect the gut microbiome and metabolic health. *Am J Physiol Endocrinol Metab* 2024;327:E89–102.
102 Moawad MH-E, Alkhawaldeh IM, Naswhan AJ. Efficacy of probiotics supplementation in amelioration of celiac disease symptoms and enhancement of immune system. *World J Clin Cases* 2023;11:7741–4.
103 Lupu VV, Trandafir LM, Raileanu AA, *et al*. Advances in Understanding the Human Gut Microbiota and Its Implication in Pediatric Celiac Disease—A Narrative Review. *Nutrients* 2023;15:2499.
104 Wagh SK, Lammers KM, Padul MV, *et al*. Celiac Disease and Possible Dietary Interventions: From Enzymes and Probiotics to Postbiotics and Viruses. *Int J Mol Sci* 2022;23:11748.
105 Maiuolo J, Bulotta RM, Ruga S, *et al*. The Postbiotic Properties of Butyrate in the Modulation of the Gut Microbiota: The Potential of Its Combination with Polyphenols and Dietary Fibers. *Int J Mol Sci* 2024;25:6971.
106 Wang G, Ding T, Ai L. Editorial: Effects and mechanisms of probiotics, prebiotics, synbiotics and postbiotics on intestinal health and disease. *Front Cell Infect Microbiol* 2024;14:1430312.
107 Ramedani N, Sharifan A, Gholam-Mostafaei FS, *et al*. The potentials of probiotics on gluten hydrolysis; a review study. *Gastroenterol Hepatol Bed Bench* 2020;13:S1–7.
108 Thoda C, Touraki M. Probiotic-Derived Bioactive Compounds in Colorectal Cancer Treatment. *Microorganisms* 2023;11:1898.
109 Ji J, Jin W, Liu SJ, *et al*. Probiotics, prebiotics, and postbiotics in health and disease. *MedComm* 2023;4:e420.
110 Fonseca HC, de Sousa Melo D, Ramos CL, *et al*. Probiotic Properties of Lactobacilli and Their Ability to Inhibit the Adhesion of Enteropathogenic Bacteria to Caco-2 and HT-29 Cells. *Probiotics Antimicrob Proteins* 2021;13:102–12.
111 Mazziotta C, Tognon M, Martini F, *et al*. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. *Cells* 2023;12:184.

112 Azad MAK, Sarker M, Wan D. Immunomodulatory Effects of Probiotics on Cytokine Profiles. *Biomed Res Int* 2018;2018:8063647.
113 Klemenak M, Dolinšek J, Langerholc T, *et al*. Administration of Bifidobacterium breve Decreases the Production of TNF-α in Children with Celiac Disease. *Dig Dis Sci* 2015;60:3386–92.
114 Olivares M, Castillejo G, Varea V, *et al*. Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of Bifidobacterium longum CECT 7347 in children with newly diagnosed coeliac disease. *Br J Nutr* 2014;112:30–40.
115 Håkansson Å, Andrén Aronsson C, Brundin C, *et al*. Effects of *Lactobacillus plantarum* and *Lactobacillus paracasei* on the Peripheral Immune Response in Children with Celiac Disease Autoimmunity: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients* 2019;11:1925.
116 Quagliariello A, Aloisio I, Bozzi Cionci N, *et al*. Effect of Bifidobacterium breve on the Intestinal Microbiota of Coeliac Children on a Gluten Free Diet: A Pilot Study. *Nutrients* 2016;8:660.
117 Primec M, Klemenak M, Di Gioia D, *et al*. Clinical intervention using Bifidobacterium strains in celiac disease children reveals novel microbial modulators of TNF-α and short-chain fatty acids. *Clin Nutr* 2019;38:1373–81.
118 Ali B, Khan AR. Efficacy of Probiotics in Management of Celiac Disease. *Cureus* 2022;14:e22031.
119 Lionetti E, Dominijanni V, Iasevoli M, *et al*. Effects of the supplementation with a multispecies probiotic on clinical and laboratory recovery of children with newly diagnosed celiac disease: A randomized, placebo-controlled trial. *Dig Liver Dis* 2023;55:1328–37.
120 Smecuol E, Hwang HJ, Sugai E, *et al*. Exploratory, Randomized, Double-blind, Placebo-controlled Study on the Effects of Bifidobacterium infantis Natren Life Start Strain Super Strain in Active Celiac Disease. *J Clin Gastroenterol* 2013;47:139–47.
121 Pinto-Sánchez MI, Smecuol EC, Temprano MP, *et al*. Bifidobacterium infantis NLS Super Strain Reduces the Expression of α-Defensin-5, a Marker of Innate Immunity, in the Mucosa of Active Celiac Disease Patients. *J Clin Gastroenterol* 2017;51:814–7.
122 Francavilla R, Piccolo M, Francavilla A, *et al*. Clinical and Microbiological Effect of a Multispecies Probiotic Supplementation in Celiac Patients With Persistent IBS-type Symptoms: A Randomized, Double-Blind, Placebo-controlled, Multicenter Trial. *J Clin Gastroenterol* 2019;53:e117–25.
123 Nikoloudaki O, Celano G, Polo A, *et al*. Novel probiotic preparation with *in vivo* gluten-degrading activity and potential modulatory effects on the gut microbiota. *Microbiol Spectr* 2024;12:e03524-23.
124 Ramedani N, Sharifan A, Nejad MR, *et al*. Influence of a combination of three probiotics on wheat dough fermentation; new therapeutic strategy in celiac disease. *Food Measure* 2024;18:2480–8.
125 Feruś K, Drabińska N, Krupa-Kozak U, *et al*. A Randomized, Placebo-Controlled, Pilot Clinical Trial to Evaluate the Effect of Supplementation with Prebiotic Synergy 1 on Iron Homeostasis in Children and Adolescents with Celiac Disease Treated with a Gluten-Free Diet. *Nutrients* 2018;10:1818.
126 Marciano R, Santamarina AB, de Santana AA, *et al*. Effects of prebiotic supplementation on the expression of proteins regulating iron absorption in anaemic growing rats. *Br J Nutr* 2015;113:901–8.
127 Drabińska N, Krupa-Kozak U, Abramowicz P, *et al*. Beneficial Effect of Oligofructose-Enriched Inulin on Vitamin D and E Status in Children with Celiac Disease on a Long-Term Gluten-Free Diet: A Preliminary Randomized, Placebo-Controlled Nutritional Intervention Study. *Nutrients* 2018;10:1768.
128 Freire R, Ingano L, Serena G, *et al*. Human gut derived-organoids provide model to study gluten response and effects of microbiota-derived molecules in celiac disease. *Sci Rep* 2019;9:7029.
129 Conte M, Nigro F, Porpora M, *et al*. Gliadin Peptide P31-43 Induces mTOR/NFkβ Activation and Reduces Autophagy: The Role of *Lactobacillus paracasei* CBA L74 Postbiotc. *Int J Mol Sci* 2022;23:3655.
130 Gargalionis AN, Papavassiliou KA, Papavassiliou AG. mTOR Signaling: Recent Progress. *Int J Mol Sci* 2024;25:2587.
131 Martorell P, Alvarez B, Llopis S, *et al*. Heat-Treated *Bifidobacterium longum* CECT-7347: A Whole-Cell Postbiotic with Antioxidant, Anti-Inflammatory, and Gut-Barrier Protection Properties. *Antioxidants (Basel)* 2021;10:536.