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# Review article: exposure to microbes and risk of coeliac disease

Ketil Størdal[1,2] | Christian Kahrs[3] | German Tapia[2] | Daniel Agardh[4] | Kalle Kurppa[5,6] | Lars C. Stene[2]

[1]Pediatric Research Institute, The Faculty of Medicine, University of Oslo, Oslo, Norway

[2]Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway

[3]Department of Pediatrics, Østfold Hospital Trust, Grålum, Norway

[4]Lund University Hospital, Lund, Sweden

[5]Center for Child Health Research, Tampere University and Department of Pediatrics, Tampere University Hospital, Tampere, Finland

[6]The University Consortium of Seinäjoki and Department of Pediatrics, Seinäjoki Central Hospital, Seinäjoki, Finland

**Correspondence**
Ketil Størdal, Pediatric Research Institute, The Faculty of Medicine, University of Oslo, Oslo, Norway.
Email: ketil.stordal@gmail.com

## Summary

**Background:** Coeliac disease is an immune-mediated intestinal disease characterised by lifelong intolerance to dietary gluten in genetically predisposed individuals. Microbial factors including infections or bacterial microbiota have long been suspected to be involved in the aetiology, but the scientific literature on the topic is scattered and heterogeneous.

**Aims:** To review human observational studies on microbes and coeliac disease

**Methods:** We identified 135 publications judged relevant. Most studies were cross-sectional, and prone to reverse causation and other biases. Only a few were prospective. Cohort studies and longitudinal studies that have sampled biological specimens before disease onset are emphasised in the review.

**Results:** Infections during early childhood were associated with an increased risk of subsequent coeliac disease in nine studies , whereas maternal infections during pregnancy did not show a clear association. For the most frequently studied microbial factors, some evidence for an association was found, including *Helicobacter pylori* (four out of 16 studies), adenovirus (two out of nine studies) and enterovirus (two out of six studies). Rotavirus infections have been associated with disease development, and rotavirus vaccination may reduce the risk. Among the many studies of gut microbiota, most were cross-sectional and, therefore, potentially influenced by reverse causation. Only two smaller prospective case-control studies with sampling before disease onset were identified; they reported inconsistent findings regarding the faecal microbiome.

**Conclusions:** Several microbes are potentially linked to coeliac disease. As microbial factors are amenable to interventions, larger prospective studies are still warranted.

The Handling Editor for this article was Professor Jonathan Rhodes, and this uncommissioned review was accepted for publication after full peer-review.

  

## 1 | INTRODUCTION

Coeliac disease (CD) is defined as a chronic immune-mediated enteropathy which is precipitated by the intake of gluten in genetically predisposed individuals.[1] The prevalence of CD is increasing worldwide, which is probably attributed to increased recognition as well as a true increase, as demonstrated in population-based screening studies.[2-4]

Genetic factors are clearly important for CD to develop.[5-7] Only individuals carrying the HLA-DQ2 or DQ8 haplotypes seem to develop CD,[8] but these alleles are also highly prevalent in the general population of whom the majority will maintain tolerance towards gluten. HLA DQ2 or DQ8 molecules and the modification of certain proline-rich parts of the gluten protein by the enzyme tissue transglutaminase (tTG) are cornerstones in the understanding of CD aetiology.[9,10] In addition, more than 40 genetic variants outside the HLA region have been identified, with markedly smaller effects on the risk of CD compared to HLA.[11,12] Interestingly, many of the non-HLA SNPs are located in regulatory regions of genes involved in immunity and response to microbes.[13] Thus, recent genetic developments point towards an interaction between genes and microbes in the pathogenesis of CD.

The rapid change in occurrence of CD over time cannot be attributed to genes, and clearly indicates a role of environmental factors in disease development. Attempts to identify these environmental factors have in the past focused on infant diet including breastfeeding and timing of gluten introduction[14] and, more recently, on the amount of gluten in early childhood.[15,16]

The gut harbours trillions of microbes, many of which are thought to play an important role in health and disease.[17] The interaction between nutrients and microbes is complex: Microbes may modify the immunogenicity of nutrients including gluten peptides, and the microbiome is also able to modulate immune responses. Conversely, the diet modifies the microbiome.[17] It has been hypothesised that gluten exposure, alone or together with other factors, leads to lifelong gluten intolerance partially through microbial pathways. An interaction between enteric viruses and bacteria is a recent field of research, adding complexity to the role of microbes in disease and health.[18,19]

In a recent experimental study of a rodent model, infection with reovirus was shown to suppress regulatory T-cell conversion and induce Th1 immunity towards dietary antigens.[20] Murine norovirus was shown to induce Th1 immunity, and signs of loss of tolerance in transcriptional profiling from mesenteric lymph nodes was observed.[21] In addition, bacterial peptides from commensal gut bacteria share homology with immunogenic gluten peptides, and were able to activate gliadin-reactive T cells from CD patients.[22] This cross-reaction suggests that microbial exposure is a potential environmental factor in the aetiology of CD. Though the molecular mechanism linking microbes to development of CD is outside the scope of this review, there is an increasing recognition that host genetics, gut microbes and dietary gluten can interact in CD development.

Although CD can occur at any age, there is a paucity of longitudinal screening studies in adults. Prospective studies with repeated serological screening of children at genetic risk indicate that the majority of cases develop CD during preschool age.[23,24] The peak incidence of developing autoantibodies against tTG, the first sign of the peripheral autoimmune response in CD, occurs already at 2-3 years of age.[15] This suggests that the search for environmental exposures should be focused on early life (Figure 1).

The time lag from seroconversion to diagnosis opens the possibility that factors observed at diagnosis could be a consequence of undetected disease as well as being a cause.[23,25] Thus, prospective studies with sample and data collection before development

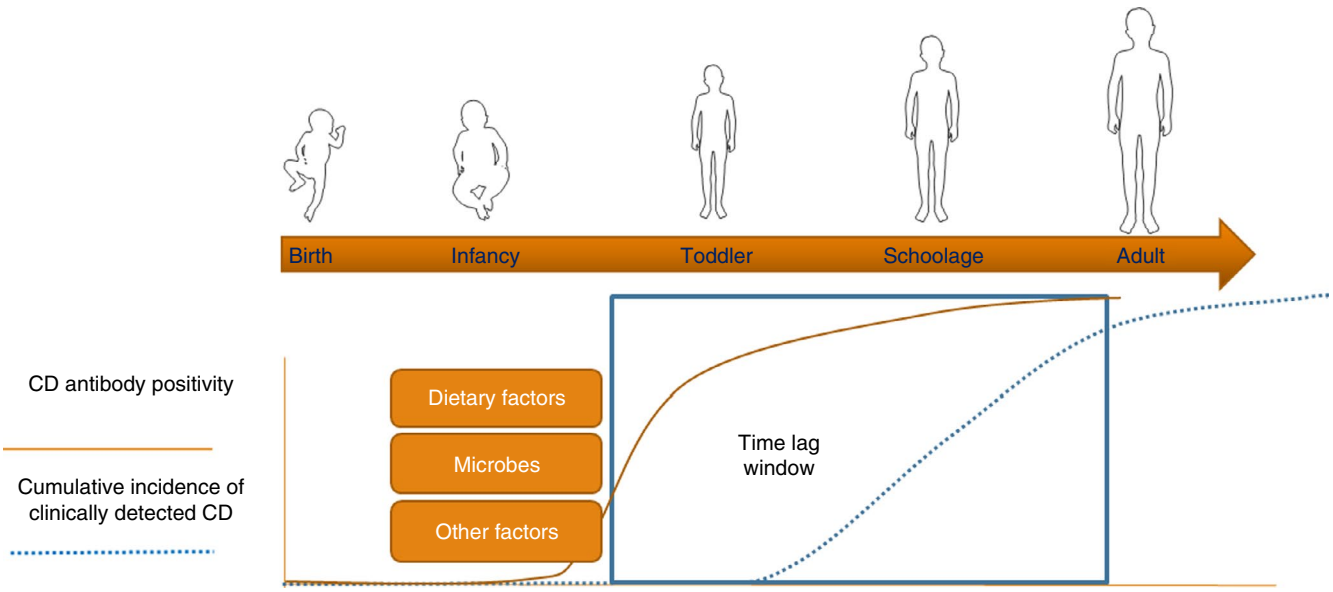


**FIGURE 1** Succession of potential environmental influences and events leading to CD with a frequently observed extended time lag between appearance of CD antibodies and clinical diagnosis

of antibodies and repeated antibody screening are highly valuable (Figure 1). The wide range in the clinical picture from asymptomatic to severe malabsorption also hampers the study of temporal environmental factors.

Here we aimed to review human studies of microbial factors as potential aetiological factors in CD, with emphasis on results from longitudinal studies that have sampled biological specimens before disease onset.

## 2 | SEARCH STRATEGY AND SELECTION CRITERIA

We followed the PRISMA guidelines for reviews.

References for this review were identified through searches of PubMed with the search terms "Coeliac disease" OR "celiac disease" AND "infection*" OR "microbiota*" OR "microbe*" OR "virus*" OR "bacteri*" OR ""microorganism*" OR "parasite*" OR "fung*" OR "helicobacter" until April 1st 2020. Only papers published in English and containing original data from human studies were reviewed. Studies reporting infections after a diagnosis of CD were not included.

The final list of studies to review was generated on the basis of originality and relevance to the scope of this review. In our literature search 812 publications were identified, 227 were selected after the initial screen and 135 retained in the final screen (Supplement for full list of references identified and Figure 2 for a flow chart of publication selection). Furthermore, we identified 43 relevant additional articles through searches of reference lists in the identified publications as well as the authors' own files.

## 3 | INFECTIOUS EPISODES

Studies from several countries have reported an association between general infections and CD risk. Studies from Sweden reported an increased risk of CD in children who had a register-based diagnosis of systemic neonatal infection[26] and a parent-reported infection concurrent with gluten introduction.[27] In the population-based nation-wide Norwegian Mother and Child study, a higher frequency of parentally reported infections before 18 months was associated with increased risk of CD, with similar risk estimates for gastrointestinal or respiratory infections.[28] This finding was later corroborated with German register data on medically attended infections the first year of life.[29] Again, both gastrointestinal and respiratory infections were significantly more frequent in individuals who later developed CD.[29] In a birth cohort from Finland and Estonia, children who developed CD by the age of 3 years had a higher number of infections the first year of life, but similar frequencies thereafter.[30] In the TEDDY cohort (The Environmental Determinants of Diabetes in the Young), a multinational cohort of children carrying HLA susceptibility haplotypes for CD, parental reports of an gastrointestinal infectious episode were positively associated with the risk of CD autoimmunity three months prior to seroconversion. In TEDDY, CD autoimmunity is defined as two consecutive blood samples with tTG IgA above the cut-off limit. The risk was further modified by HLA genotype, infant gluten consumption, breastfeeding and rotavirus vaccination.[31] Two retrospective case-control studies from Sweden found infections <6 months[32] and urinary tract infections[33] as significant risk factors for later CD. In a questionnaire-based retrospective survey from the US, ear infections before the age of 2 years were significantly more frequent in children with CD compared to controls.[34]

In contrast, maternal infections during pregnancy have not clearly been associated with later risk of CD in offspring in two prospective studies.[35,36]

Undiagnosed CD could predispose to infections, and thereby cause reverse associations. However, studies restricting the exposure period to an early time window with a minimal risk of CD should avoid a potential reverse causality. A study of military

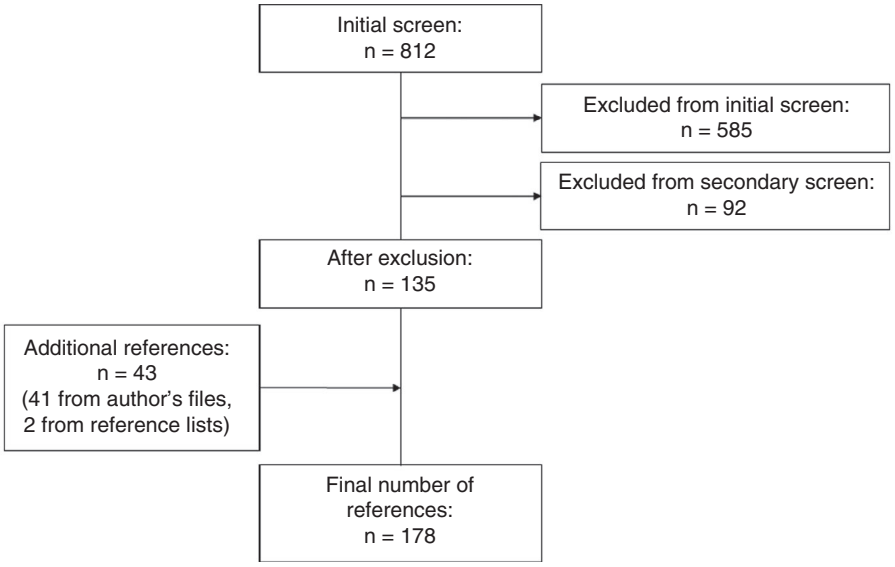


**FIGURE 2** Flow chart for selection of publications for the review

personnel from US found a higher incidence of CD at 4 years after a medically attended gastrointestinal infection.[37] In a follow-up study, the risk was attributed to campylobacter infections, which was the most frequent causative bacterial agent identified.[38] Such a finding could be biased if infections cause symptoms indistinguishable from CD, leading to diagnostic work-up without being part of the aetiology.

Register-based studies capture only infections severe enough to cause a health care contact, whereas cohort studies may capture less severe infections.[39] Subclinical infections are not even captured in studies relying on reporting from patient or caregivers. Studies with prospective sampling of biological specimens provide opportunities to study subclinical infections and allow for detection of specific microbes.

## 4 | SPECIFIC MICROBES

### 4.1 | Rotavirus

Infections with rotavirus as characterised by increase in antibody titres were associated with CD in a US cohort with increased hereditary and/or HLA risk for CD and type 1 diabetes (Table 1).[40] A cross-sectional study on a peptide library screened against sera from individuals with untreated CD identified a peptide with shared homology with the rotavirus major neutralising protein VP-7.[41] Antibodies reactive against the VP7 region of the virus were more common in cases than in controls,[42] but this finding was not corroborated in a more recent study.[43]

In a follow-up of a randomised double-blind controlled trial from the early phases of rotavirus vaccination, those with active vaccine had almost half the prevalence of diagnosed CD at 11-14 years

**TABLE 1** Rotavirus and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Stene, 2006. USA.[40] | Prospective study of children with CD (n = 54) and controls (n = 108) in a high-risk cohort for CD and type 1 diabetes. Antibody screening for rotavirus infection at 9, 15 and 24 mo and annually thereafter. | Infections with rotavirus as characterised by increase in antibody titres were associated with CD. Rate ratio for trend per increase in number of infections 1.94, 95% CI 1.04-3.61, $P = 0.037$. |
| Zanoni, 2006. Italy.[41] | Cross-sectional study of children and adults with U-CD (n = 22) and T-CD (n = 38). A random peptide library was screened against sera from cases and controls. | A peptide with shared homology with the rotavirus major neutralizing protein VP-7 was recognised by serum immunoglobulins of patients with U-CD but not by those with T-CD. |
| Dolcino, 2013. Italy.[42] | Children with type 1 diabetes and CD (n = 26) and controls with type 1 diabetes and no CD (n = 37). Serum samples before and after diagnosis available for eight CD patients. Serological screening for antibodies against the rotavirus VP-7 peptide. | Antibodies reactive against the VP7 region of the rotavirus were more common in cases (80%) than in controls (27%). Six of the eight with serial samples had antibodies present before the CD diagnosis. |
| Ziberna, 2016. Italy.[43] | Cross-sectional study of children and young adults with biopsy-proven CD (n = 118), children with potential CD (n = 46), 32 children with other gastrointestinal diseases, children with no CD (n = 107) and 107 blood donors. Serological screening for antibodies against the rotavirus VP-7 peptide. | Antibody reactivity in 18% of CD patients in both paediatric (16%) and adult (27%) control groups, with no statistically significant difference (CD vs HC children $P = 0.6$, CD vs HC adults $P = 0.1$). |
| Vaccine studies | | |
| Vaarala, 2017. Finland.[45] | Population-based study in a cohort born in 2009-2010 comparing the risk of CD as registered in national patient registers (2009-2014) among vaccinated (n = 94,437) and unvaccinated (n = 27 213) children. | Vaccinated children had a non-significantly lower risk of 293 CD (n = 201, 0.21%) compared to non-vaccinated (n = 92, 0.33%) children after 4-6 y follow-up (adjusted OR 0.87, 95%CI 0.65-1.17). |
| Hemming-Harlo, 2019. Finland.[44] | Follow-up of a randomised double-blind controlled vaccine trial with RotaTeq from 2001 to 2003 with parental questionnaires reporting diagnosis of CD returned by 30% in 2015. | Lower prevalence of CD in the active vaccine group (n = 19/3184, 0.6%) compared to the placebo group (n = 29/2580, 1.1%) at 11-14 y age ($P = 0.027$). |
| Kemppainen, 2017. Multinational.[31] | The multinational TEDDY cohort (n = 6,327) with serial screening for coeliac disease antibodies. 11% (n = 732) developed coeliac disease autoimmunity (CDA) by the age of 4 y. | Lower risk for CDA in children vaccinated against rotavirus, but only when gluten was introduced before the age of 6 mo (Adjusted HR, 0.57; 95% CI 0.37-0.88). Gastrointestinal infections increased the risk of CDA within the following 3 mo only in unvaccinated children (adjusted HR, 1.46; 95% CI, 1.03-2.09) and not in vaccinated children (adjusted HR, 0.81; 95% CI, 0.51-1.28. |

Abbreviations: CDA, coeliac disease autoimmunity; CI, confidence interval; GFD, gluten-free diet; HC, healthy controls; HR, hazard ratio; OR, odds ratio; T-CD, treated coeliac disease; U-CD, untreated coeliac disease.

compared to the placebo group.[44] In a later population-based study the risk of CD was not significantly lower in vaccinated children compared to non-vaccinated children.[45] A sub-analysis from the TEDDY cohort demonstrated a lower risk in children vaccinated against rotavirus, but only when gluten was introduced before age of 6 months.[31]

## 4.2 | Enterovirus

In cross-sectional studies investigating enterovirus in duodenal biopsies by RT-PCR, in situ hybridisation and immunohistochemistry, one study found neither cases with CD nor controls to be positive[46] whereas another study found slightly higher frequencies in cases with CD compared to controls (Table 2).[47] Furthermore, neither cases nor controls had enterovirus in nasal/stool swabs restricted to the first 6 months of life, and antibodies against enterovirus at diagnosis did not differ between cases and matched controls.[48] These findings are not surprising because enterovirus infections are uncommon in early infancy but nearly ubiquitous before the age of three.

In a recent Norwegian study, enterovirus was more frequent in repeated stool samples from cases compared to matched controls before the appearance of serum IgA-class antibodies to tTG (tTG-IgA) as the first sign of CD.[49] Severity of infection as measured by viral load, duration of shedding and symptoms was also associated with CD. This observation was further supported by the TEDDY study, which also found an interaction with the amount of dietary gluten.[50] In contrast, intrauterine enterovirus infections (antibodies in cord blood) were not associated with CD.[51]

Recently parechovirus, another small RNA virus related to enterovirus (family *Picornaviridae*), was found to be significantly more frequent in repeated stool samples from cases vs matched controls in the same cohort as the initial enterovirus study.[52] Co-infections with parechovirus and enterovirus had the strongest association with later CD.

## 4.3 | Adenovirus

A peptide sequence homology of wheat gliadin and human adenovirus 12 (Ad12) was described for the first time in 1984 in animal models.[53,54] The same group later reported a higher sero-prevalence of antibodies to Ad12 in CD cases compared to controls (Table 3),[55] but findings in two following studies were ambiguous.[56,57] Four subsequent studies have found similar prevalence of positivity for adenovirus in duodenal biopsies among CD cases and controls.[58-61] Recent studies using repeated stool samples did

**TABLE 2** Enterovirus and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Mercalli, 2012. Italy.[46] | Cross-sectional case-control study of patients with CD (n = 27), and healthy controls (n = 21). Duodenal biopsies tested for enterovirus RNA by radioactive I -situ hybridisation and RT-PCR, and for enterovirus proteins by immunostaining. | Neither cases with CD nor controls was found to be positive for enterovirus. |
| Oikarinen, 2012. Finland.[47] | Cross-sectional case-control study from patients with CD (n = 40) and HC (n = 41). Duodenal biopsies analysed for enterovirus using in situ hybridisation (ISH), RT-PCR and immunohistochemistry. | Enterovirus RT-PCR not different in manifest CD vs HC (15% and 10%, respectively). Enterovirus (ISH) found in 45% and 29%, respectively (n.s.). |
| Simre, 2018. Estonia/Finland.[48] | Prospective matched study of children with CD (n = 29) and HC (n = 29). RT-PCR of nasal swabs and stool samples taken at the age of 3-6 mo and antibodies in serum samples taken at diagnosis. | Enterovirus in nasal/stool swabs was not found in neither cases and matched controls. Antibody positivity did not differ ($P = 0.93$). |
| Kahrs, 2019. Norway.[49] | Prospective matched case-control study (n = 25 cases, n = 49 controls, mean age 9.9 y) nested in a prospective birth cohort with increased genetic risk of CD and serial screening for CD. Monthly stool samples from 3 to 36 mo (n = 2,135) screened for enterovirus. | Enterovirus more frequent in repeated stool samples from cases compared to matched controls before tTG-IgA antibodies developed as the first serological sign of CD (adjusted odds ratio 1.49, 95% CI 1.07-2.06). Severity of infection (viral load, duration of shedding and symptoms) was also associated with CD. |
| Lindfors, 2019. Multinational.[50] | Prospective matched case-control study (TEDDY cohort, n = 83 pairs) with serial screening for coeliac disease antibodies. Metagenomic screening of serial stool samples from 0 to 2 y age. | Enterovirus more frequent in cases vs controls (adjusted OR 2.56, 95% CI 1.19-5.51). |
| Carlsson, 2002. Sweden.[51] | Prospective case-control study of children with CD before the age of 15 y (n = 76) and healthy controls (n = 327). Cord blood IgA, IgG and IgM against enteroviruses. | Intrauterine enterovirus infections were not associated with later CD risk of the offspring. |

Abbreviations: CDA, coeliac disease autoimmunity; CI, confidence interval; GFD, gluten-free diet; HC, healthy controls; OR, odds ratio; RT-PCR, real-time polymerase chain reaction; T-CD, treated coeliac disease; U-CD, untreated coeliac disease.

**TABLE 3** Adenovirus and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Kagnoff, 1987. USA.[55] | Cross-sectional study of adults and children with U-CD (n = 18), T-CD (n = 62) and controls (n = 135) from London adult (cohort 1), London paediatric (cohort 2) and US adult (cohort 3). Antibodies against Ad12 (a region different from,[54] Ad18 and Echovirus 11 tested in cases and controls. | Significantly higher prevalence of antibodies against Ad12 in U-CD vs T-CD and controls (cohort 1), and in T-CD vs controls (cohort 2 and 3). Antibody positivity against Ad18 and Echovirus 11 not significantly different. |
| Howdle, 1989. UK.[56] | Cross-sectional study of adult CD patients (7 untreated and 16 treated) and 10 healthy controls. Antibodies against Ad12 Elb protein assayed in sera. | None of the CD patients had antibodies against Ad12, one of the healthy controls weakly positive. |
| Lähdeaho, 1993. Finland.[57] | Cross-sectional study of children with U-CD (n = 44), dermatitis herpetiformis (DH, n = 16) and 60 matched healthy controls. Serum antibodies to synthetic peptides derived from an early E1b protein of Ad12 and A gliadin tested. | Both U-CD and DH had significantly ($P < 0.001$) higher IgG antibody levels to the Ad12 E1b peptide than the controls. |
| Carter, 1989. UK.[58] | Cross-sectional study of adults with U-CD (n = 2), T-CD (n = 11) and HC (n = 13). Duodenal biopsies assayed for Ad12 and Ad41 DNA by Southern blot technique. | No signs of persistent adenovirus infection neither in cases nor controls. |
| Mahon, 1991. UK.[59] | Cross-sectional study of children and adults with U-CD (n = 7), T-CD (n = 11) and HC (n = 24). DNA isolated from biopsy samples and analysed by PCR for adenovirus 12 DNA encoding the E1B-58 kDa protein. | Ad12 DNA found in 5/18 with CD and 2/24 HC. |
| Vesy, 1993. USA.[60] | Cross-sectional study of children with CD (n = 19), adults with CD (n = 14) and controls. DNA isolated from biopsy samples and analysed by PCR for Ad12, CMV and HSV. | Ad12 DNA in 2/14 adults and in 0/19 children with CD. Ad12 not found in any of the control group patients. |
| Lawler, 1994. Ireland.[61] | Cross-sectional study of children with CD and diagnosis <1 y age (n = 10) and non-CD controls (n = 7). Adults with CD (n = 17) and non-CD controls (n = 16). DNA against Ad12 isolated from duodenal biopsies and analysed by PCR. | Ad12 positive in 3/10 childhood CD patients and 1/7 controls. Ad12 sequences in 3/17 adults with CD and in 5/16 adult controls. No significant differences. |
| Kahrs, 2019. Norway.[49] | Prospective matched case-control study (n = 25 cases, n = 49 controls, mean age 9.9 y) nested in a prospective birth cohort with increased genetic risk of CD and serial screening for CD. Monthly stool samples from 3 to 36 mo (n = 2006) screened for adenovirus. | Similar frequency of adenovirus infections in cases and controls before tTG-IgA antibodies developed (adjusted OR 0.82, 0.49-1.38; $P = 0.46$). |
| Lindfors, 2019. Multinational.[50] | Prospective matched case-control study (TEDDY cohort, n = 83 pairs) with serial screening for coeliac disease antibodies. Metagenomic screening of serial stool samples from 0 to 2 y age. | Adenovirus similar between cases and controls (adjusted OR 1.41, 95% CI 0.99-2.02). Lower risk for CDA if adenovirus infection <1 y (adjusted OR 0.69, 95% CI 0.48-0.99, $P = 0.04$). |

Abbreviations: Ad12, adenovirus 12; CDA, coeliac disease autoimmunity; CI, confidence interval; HC, healthy controls; OR, odds ratio; RT-PCR, real-time polymerase chain reaction; T-CD, treated coeliac disease; U-CD, untreated coeliac disease.

not find adenovirus positivity to predict later CD,[49,50] or found indications of protective association of virus positivity before the age of 1 year.[50]

## 4.4 | Respiratory viruses

Children with CD diagnosis before the age of 2 years were more likely to have had a hospital-attended infection with respiratory syncytial virus prior to CD diagnosis than controls in a register-based study (OR 1.46 [95% CI 1.03-2.07]).[62] After seasonal or pandemic influenza an increased risk of a new diagnosis of CD was found in a nation-wide register-based study (HR 1.29 (95% CI, 1.21-1.38).[63] In a prospective matched case-control study with PCR of nasal swabs collected at 3-6 months, rhinovirus was found in 5/18 children with CD (28%) compared to 0/16 in controls ($P = 0.05$).[48]

## 4.5 | Hepatitis C

A higher prevalence of CD-associated serum endomysium antibodies was reported in patients with hepatitis C virus (HCV) compared to HCV negative blood donors (Table 4).[64,65] Three other studies of HCV patients have however not found such an association.[66-68] Interestingly, one retrospective study reported α-interferon administered to treat HCV infections to precipitate symptoms or antibody production typical for CD.[66] Thus, an association could be due to infection as well as treatment. However, in two studies performing CD screening before and after treatment

**TABLE 4** Hepatitis C and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Fine, 2001. USA[65] | Cross-sectional study of consecutive cases with HCV (n = 259) autoimmune liver disease (n = 59), other hepatic diseases (n = 137), various GI syndromes (n = 356) and healthy controls (n = 221). Examined for tTG-IgA, EMA-IgA and for anti-gliadin IgA and IgG antibodies. Patients with coeliac disease antibodies underwent duodenal biopsy. | CD diagnosed in three patients with HCV (1.2%) and in two with autoimmune liver disease (3.4%). Two out of three with HCV had not been given α-interferon for HCV. One of HC (0.4%) also had CD and was found to have hepatitis C. Statistically significant difference between HCV and HC ($P = 0.02$). |
| Vivas, 2003. Spain.[68] | Cross-sectional study of cases with HCV (n = 102) and blood donors (n = 165). Examined for the presence of tTG-IgA, EMA-IgA and for anti-gliadin IgA and IgG antibodies. | Elevated tTG-IgA in none of the HCV cases and 1/165 blood donors. |
| Thevenot, 2007. France.[67] | Cross-sectional study of 624 consecutive HCV-positive outpatients. Tested for EMA-IgA, anti-gliadin IgA and IgG antibodies. Gastroscopy with duodenal biopsies in 25 out of 39 with suspected CD. | Isolated EMA-IgA in 0.16%, anti-gliadin IgA and IgG in 5.7% and 4.4% respectively. None were diagnosed with CD. |
| Ruggeri, 2008. Italy.[64] | Cross-sectional study of cases with hepatitis C liver disease (n = 244), with liver disease of other causes (n = 121) and 1230 blood donors. Examined for the presence of tTG-IgA and EMA-IgA antibodies. | tTG-IgA and EMA in 5/244 (2%) HCV-patients, 1/121 (0.8%) non-HCV-patients and 2/1,230 (0.16%) blood donors, significant difference between HCV-patients and blood donors (Odds ratio 12.8; 95% Confidence Interval 2.4-66). α-interferon was given after enrolment to 42 HCV-patients of whom none developed CD. |
| Hernandez, 2008. USA.[66] | Cross-sectional study of cases with hepatitis C liver disease (n = 195), other liver diseases (n = 19) and healthy controls (n = 80). Tested for EMA-IgA, tTG-IgA, anti-gliadin IgA and IgG antibodies. In addition, HCV screening was performed of CD patients from a database. | tTG-IgA in 2/195 HCV patients (1%), with negative EMA. None of these two had evidence of coeliac disease on duodenal biopsy. None in the control groups had CD antibodies. From the database of 895 CD patients, six (0.68%) had HCV, which was comparable to the background population. Three were diagnosed with CD during or after α-interferon therapy. |
| Gravina, 2012. Italy.[69] | Cross-sectional study of adults with hepatitis C liver disease (n = 210) screened for CD. Adults with CD (n = 194) were screened for HCV. | None of the HCV patients had CD antibodies. 3/194 (1.5%) patients with CD had HCV. No control groups reported. None of the 130 patients treated with α-interferon developed CD. |

Abbreviations: EMA, endomysial antibody; HCV, hepatitis C virus; IgA, immunoglobulin A; IgG, immunoglobulin G; tTG, tissue transglutaminase.

with α-interferon none of the 172 patients developed CD during treatment.[64,69]

## 4.6 | Helicobacter pylori

The prevalence of *H. pylori* is declining over time with improved hygiene and eradication strategies due to its role in peptic ulcer disease, MALT lymphoma and gastric cancer.[70] Whether *H. pylori* and CD are associated has been extensively studied (Table 5).

A weak protective role of *H. pylori* in CD was reported in some but not all previous studies. However, since study participants are mostly enrolled from endoscopy clinics, there is always a risk of selection bias due to a high prevalence of *H. pylori* in those referred for upper endoscopy.[71-80] Studies using randomly selected controls and non-invasive methods to identify *H. pylori* have uniformly reported no significant associations.[81-86] Only two studies had a prospective design, none of which showed significant associations between *H. pylori* infection and CD.[85,86]

## 4.7 | Other microbes

In a cross-sectional Dutch study, positivity for antibodies against cytomegalovirus (CMV) was associated with a lower risk of CD autoimmunity (Table 6). Infections with Epstein-Barr virus (EBV) and herpes simplex type 1 (HSV1) were not associated with the risk of CD, but the combination of either of the herpesviruses CMV/EBV/HSV1 conferred a reduced risk.[87] Supporting this observation, an inverse association with CMV and rubella but unclear results for EBV was found.[88] The prevalence of CMV DNA in biopsies from CD cases and healthy controls was similar.[60] In a group with congenital rubella

**TABLE 5** *Helicobacter pylori* and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Control group from endoscopy clinics/invasive methods | | |
| Diamanti, 1999. Argentina.[71] | Adults with CD (n = 104, 80 newly diagnosed) and controls (n = 114) referred for similar symptoms. HP diagnosed by histology or serology (incomplete screening in the control group). | Similar prevalence in CD (87%) compared to non-CD controls (89%). |
| Ciacci, 2000. Italy. [72] | Adults with CD and controls (total n = 263) referred for endoscopy in a prospective data collection. | Lower prevalence of HP in untreated CD (20.7%) compared with treated CD (32.4%) and non-CD controls (55.3%), $P = 0.001$. |
| Aydogdu, 2008. Turkey.[73] | Children with CD (n = 96) and non-CD controls (n = 235). | Similar prevalence of HP in CD cases (22%) and non-CD controls (24%). |
| Lebwohl, 2013. USA.[74] | Biopsies from a pathology bank (n = 136,179), CD was found in 2% (n = 2,689). Adjustment for age, gender, racial, ethnic and socioeconomic factors. Excluded patients with ulcer or malignancy. | HP was found in 4% with CD and 8% of non-CD controls. Adjusted OR 0.48 (95%CI 0.40-0.58). |
| Lasa, 2015. Argentina.[75] | Adults with CD (n = 72) or non-CD controls (n = 250) who were referred for endoscopy. | Prevalence of HP lower in CD (12.5%) vs non-CD controls (30%), OR 0.33 (95% CI 0.15-0.71) |
| Simondi, 2015. Italy.[76] | Adults with CD (n = 154) vs non-CD controls suffering from constipation (n = 404). | Similar prevalence of HP in CD (36%) compared to non-CD controls (41%). |
| Uyanikoglu, 2016. Turkey.[77] | Adults with CD (n = 31) vs non-CD controls (n = 592) from an endoscopy clinic. | Similar prevalence of HP in CD (48%) compared to non-CD controls (53%), n.s. |
| Narang, 2017. India.[78] | Children with CD (n = 324) vs non-CD controls referred for endoscopy (n = 322). No description of control group selection. | Lower prevalence of HP in children with CD (11%) compared to non-CD controls (50%). |
| Lucero, 2017. Chile.[79] | Children and adults with active CD (n = 29), potential CD (n = 37) and non-CD controls (n = 50). | Similar prevalence of HP positivity with active CD (34%), potential CD (30%) and non-CD (40%). The virulence factor CagA more common in HP infected with potential CD compared to active CD, and less severe villous atrophy in CagA positives. |
| Agin, 2019. Turkey.[80] | Children with CD (n = 256) and children with dyspepsia as controls (n = 1012) tested for HP in duodenal samples. | Similar prevalence of HP found in CD (27.4%) and non-CD controls (26.7%), n.s. |
| Control group from non-endoscopy settings/non-invasive methods | | |
| Crabtree, 1992. UK.[81] | Adults with CD (n = 99) and 250 age-matched controls (n = 250) tested with HP serology. | Similar prevalence of seropositivity for HP among CD cases (29%) and controls (30%). |
| Luzza, 1999. Italy.[82] | Children with CD (n = 81) and non-CD controls (n = 81) tested with HP serology. | Similar prevalence of HP positivity in CD cases (19%) and controls (17%). |
| Konturek, 2000. Germany.[83] | Adults with CD (n = 91) vs healthy age- and sex-matched non-CD controls (n = 40) tested with HP serology. | Similar prevalence of HP in CD cases (26%) vs controls (20%), OR 1.44 (95% CI 0.58-3.44). |
| Jozefczuk, 2015. Poland.[84] | Children with CD (n = 74) and age-matched non-CD controls (n = 296) tested with breath test. | Similar prevalence of HP in CD cases (5.4%) and controls (6.8%), $P = 0.57$. |
| Bartels, 2016. Denmark.[85] | Prospective study of a cohort followed for 6 y for development of CD after a breath test positive (n = 11 830) or negative (n = 48 879) for HP. | Prevalence of CD in HP positives 0.05% compared with 0.09% among HP negatives (OR 0.65 [CI: 0.24-1.73] after adjustment for age and sex). |
| Dore, 2018. Italy.[86] | Prospective study of adults with genetic risk for CD followed for HP positivity in groups with (n = 270) or without (n = 127) CD. | Similar prevalence of HP in CD cases (32%) and controls (36%, OR 0.81 [0.52-1.26]). |

Abbreviations: CI, confidence interval; HP, *Helicobacter pylori*; N.s., not significant; OR, odds ratio.

syndrome (n = 25) or exposure to rubella in utero without clinical features (n = 12), none of the 37 cases examined developed CD.[89] Antibodies against *Toxoplasma gondii* and *Treponema pallidum* were not significantly associated with CD.[88]

A modest association with a clinical diagnosis of infection with *Borrelia burgdorferi* both prior to and after a diagnosis of CD was found in a Swedish study, which could, however, be explained by a surveillance bias.[90] Serum anti-Saccharomyces cerevisiae antibodies (ASCA) were significantly more prevalent and in higher titres in patients with untreated CD compared to healthy controls,[91] but significantly elevated only in active CD and not detected in treated CD and healthy controls in another study.[92] *Mycobacterium avium*

**TABLE 6** Other microbes and coeliac disease (CD)

| Reference | Setting and methods | Finding |
|---|---|---|
| Vesy, 1993. UK.[60] | Cross-sectional study of children with CD (n = 19), adults with CD (n = 14), patients with duodenitis (n = 22) and HC (n = 40). DNA isolated from biopsy samples and analysed by PCR for CMV and HSV. | CMV in 1/14 adults and 0/19 children with CD, and HSV in 1/14 adults and 2/19 children with CD. CMV and HSV not found in any of the control group patients. |
| Simre, 2019. Estonia/Finland.[48] | Prospective matched study of children with CD (n = 29) and HC (n = 29). IgG antibodies against CMV and EBV in serum samples taken at diagnosis. | No difference in CMV or EBV IgG antibodies between the groups. |
| Jansen, 2016. Netherlands.[87] | Cross-sectional screening for CD by 6 y (n = 49 CDA, 31 of those with tTG-IgA < 10 X elevated among 4420 participants) in the prospective Generation R study. Serum immunoglobulin G levels against CMV, EBV and HSV1 measured by enzyme-linked immunosorbent assay at 6 y. | Positivity for cytomegalovirus (CMV) was negatively associated with the risk of high titre CDA vs HC (aOR 0.38, 95% CI 0.14-0.98). Infections with Epstein-Barr virus (EBV) and herpes simplex type 1 (HSV1) were not associated with the risk of CD, but the combination of either of the herpesviruses CMV/EBV/HSV1 conferred a reduced risk vs HC (aOR 0.38, 95% CI 0.18-0.78). |
| Plot, 2009. Israel.[88] | Cross-sectional case-control study of CD patients (n = 90) vs HC (n = 297) for serological evidence of past infection with Toxoplasma gondii, rubella virus, EBV, CMV and Treponema pallidum. | Significantly lower prevalence in CD patients vs HC for antibodies against CMV (54% vs 68%) and rubella (88% vs 95%). Non-significant differences for *Toxoplasma gondii* and *Treponema pallidum*, and unclear findings for the EBV antibodies. |
| Viskari, 2003. Finland.[89] | Case series of congenital rubella syndrome or known exposure to rubella in utero (n = 38). | None of the cases examined had CD or positive tTG-IgA. |
| Alaedini, 2016. Sweden.[90] | Registry study of CD patients (n = 15 769) and matched controls (n = 78 331). Diagnosis of Lyme's disease in national patient registers before CD diagnosis. | Borrelia infection in 25 (0.16%) before CD diagnosis and in 79 (0.5%) after CD diagnosis. Odds ratio, 1.61 (95% CI 1.06-2.47) and after the diagnosis of coeliac disease (hazard ratio, 1.82; 95% CI, 1.40-2.35) compared to matched controls. |
| Ashorn, 2008. Finland.[91] | Cross-sectional study of children and adults with U-CD (n = 134), non-CD disease controls (n = 108) and adult healthy blood donors (n = 80). Serum anti-Saccharomyces cerevisiae antibodies (ASCA) IgA and IgG antibodies in serum samples. | ASCA significantly more prevalent and in higher titres in U-CD (46%) compared to non-CD (15%) and healthy controls (0%), $P < 0.001$. |
| Biet, 2011. France.[92] | Cross-sectional study of adults with 'active' CD (n = 16), T-CD (n = 19) and healthy blood donors (n = 120). ASCA IgA and IgG antibodies in serum samples. | Significantly elevated only in active CD (7/16, 40%) and not detected in T-CD and healthy controls ($P = 0.005$). |
| Verdier, 2013. France[93] | Cross-sectional study of adults with 'active' CD (n = 23) and healthy controls (n = 45). Specific IgG and IgA response against *Mycobacterium avium paratuberculosis* | No significant differences between cases and controls. |

Abbreviations: ASCA, anti-saccharomyces cerevisiae antibodies; CMV, cytomegalovirus; EBV, Epstein Barr virus; EMA, endomysial antibody; HC, healthy controls; HSV, herpes simplex virus; IgA, immunoglobulin A; IgG, immunoglobulin G; OR, odds ratio; T-CD, treated coeliac disease; tTG, tissue transglutaminase; U-CD, untreated coeliac disease.

*paratuberculosis* was not associated with active CD in a case-control study.[93]

Inferring a causal relationship between less infections and increase in immune-mediated disease, the hygiene hypothesis was originally suggested to explain an inverse association between household size and the prevalence of childhood atopic disease.[94] Expanding on the hygiene hypothesis, experimental hookworm infection is explored as a method to suppress immune responses,[95] potentially mediated through the microbiome in CD patients.[96,97] However, the ultimate goal of inducing tolerance towards gluten was not achieved in a pilot study,[98] though a sustained open gluten challenge after infection with *Necator Americanus* indicated some benefit.[99]

## 5 | PERTURBATIONS OF THE INTESTINAL MICROBIOME

The early gut microbiome is unstable and rapidly changing before a more resilient adult-like pattern is established around the age of 3 years.[100] The composition of the microbiome in CD has been extensively studied applying culture-based methods and sequencing technology. Cross-sectional studies are prone to bias as colonisation of an already damaged mucosa imply a risk of reverse causality. Prospective studies are preferable for inferring potential direct causality.

Two recent cohort studies have followed infants at genetic risk for CD with repeated stool samples before CD developed.[101,102]

**TABLE 7** Cross-sectional studies of microbiota in duodenal biopsies in untreated (U-CD) and treated (T-CD) coeliac disease patients vs healthy controls (HC)

| Reference | Setting and methods | Findings |
|---|---|---|
| Forsberg,[105] 2004. Sweden. | Children with U-CD (n = 29), T-CD (n = 37) vs HC (n = 59). Bacteria identified by scanning electron microscopy. Glycocalyx composition and mucin and antimicrobial peptide production studied by quantitative RT-PCR, antibody and lectin immunohistochemistry. | Rod-shaped bacteria present in U-CD and T-CD but not in HC. Also distinct changes in the mucus layer and in markers of innate immunity. |
| Nadal,[106] 2007. Spain. | Children with U-CD (n = 20) and T-CD (n = 8) vs HC (n = 10). In situ hybridisation and flow cytometry. | Higher counts of total bacteria and gram-negatives in U-CD than in T-CD and HC, and the Bacteroides/Prevotella group and *E. coli* significantly more abundant in U-CD. The ratios of beneficial bacterial groups (Lactobacillus plus Bifidobacterium) to potentially harmful Gram-negative bacteria (Bacteroides–Prevotella plus *E. coli* groups) significantly lower in U-CD vs T-CD and HC. |
| Collado,[103] 2009. Spain. | Children with U-CD (n = 30), T-CD (n = 18) vs HC (n = 30). Bacterial groups quantified by real-time PCR. | Bacteroides and *Cl. leptum* groups more abundant in CD patients than in HC. E coli and Staphylococcus counts higher in U-CD than in HC, but levels were normalised on a GFD. Bifidobacterium levels lower in U-CD than in HC. |
| Ou,[107] 2009. Sweden. | Children with U-CD (n = 45) vs HC (n = 18), cultured with 16S rDNA and electron microscopy. | Rod-shaped bacteria found in CD (Clostridia and Prevotella) and not in HC. |
| Sanchez,[108] 2010. Spain. | Children with U-CD (n = 20) and T-CD (n = 12) vs age-matched HC (n = 8). PCR-denaturing gradient gel electrophoresis (DGGE) analyses by universal and group-specific primers. | Bacteroides diversity higher in HC, also higher abundance with only *B. dorei* lower in HC. Bifidobacteria diversity higher in CD vs HC. |
| Schippa,[109] 2010. Italy. | Children with CD before and after GFD (n = 20 pairs) vs HC (n = 10). 16S rDNA compared by temporal temperature gradient gel electrophoresis (TTGE). | Higher biodiversity in CD before than after GFD (T-CD), and higher in U-CD vs HC. More often *Bacteroides vulgatus* and *E. coli* in U-CD and T-CD vs HC *Bacteroides vulgatus* and *Cl. coccoides* more frequent in U-CD vs T-CD. |
| DiCagno,[104] 2011. Italy. | Children with T-CD (n = 19) and HC (n = 15). PCR-denaturing gradient gel electrophoresis (DGGE) analyses by universal and group-specific primers. | Higher diversity of Eubacteria in T-CD compared to HC. |
| Nistal,[110] 2012. Spain. | Adults and children with U-CD (n = 10) and T-CD (n = 5) vs HC (n = 5). 16S rRNA gene sequencing of extracted DNA. | Higher diversity by age. Streptococcus less abundant in adults with U-CD vs HC. No significant difference between U-CD and HC in children. |
| Cheng,[111] 2013. Finland. | Children with U-CD (n = 10) vs HC (n = 9). Bacterial phylogenetic microarray to profile the microbiota in duodenal biopsies. Expression of selected mucosa-associated genes assessed by qRT-PCR. | No overall differences in microbiota, though eight genus-like groups had different abundance. Increased expression of TLR10 and higher of TLR9, IL10, IFNγ and CXCR in CD. |
| Wacklin,[112] 2013. Finland. | Adults with CD (n = 33) and dermatitis herpetiformis (n = 6) vs HC (n = 18). PCR denaturing gradient gel electrophoresis. A subset of samples additionally by 16S ribosomal RNA gene sequencing | Lower diversity and higher abundance of Proteobacteria in CD than in DH and HC, Firmicutes dominant in DH and HC. |
| Sanchez,[113] 2013. Spain. | Children with U-CD (n = 32) and T-CD (n = 17) vs age-matched HC (n = 8). Partial 16S rRNA gene sequencing. | Higher diversity in U-CD vs T-CD and HC. Higher abundance of phylum Proteobacteria and lower abundance of the phylum Firmicutes in CD vs HC. At the family level also higher abundance of Enterobacteriaceae (esp. Klebsiella), and Staphylococcae in U-CD. Streptococcaceae less abundant in U-CD vs HC. |
| D'Argenio,[114] 2016. Italy. | Adults with U-CD (n = 20) and T-CD (n = 6) vs HC (n = 15). DNA-sequencing of ribosomal 16S. | Proteobacteria were the most abundant and Firmicutes and Actinobacteria the least abundant phyla in the microbiome profiles of U-CD patients. Members of the Neisseria genus are more abundant in U-CD patients than in the other two groups ($P = 0.03$). |
| De Meij,[115] 2016. Netherlands. | Children with U-CD vs age-matched HC (n = 21 pairs). Analysed by a 16S-23S interspacer region-based profiling method. | No significant differences between U-CD and HC. |

(Continues)

**TABLE 7** (Continued)

| Reference | Setting and methods | Findings |
|---|---|---|
| Nistal,[116] 2016. Spain. | Adults with U-CD (n = 9) vs HC (n = 9). Next-generation pyrosequencing of 16S rRNA. | No significant differences between U-CD and HC. |
| Pietz,[117] 2017. Sweden. | Children with U-CD (n = 26) and T-CD (n = 5) vs HC (n = 25). In vitro model with enteroids and polarised tight monolayers. | The interferon regulatory factor (IRF) pathway was upregulated bacteria previously identified in biopsies from U-CD patients (*Prevotella jejuni*, *Lachnoanaerobaculum umeaense*, *Actinomyces graevenitzii*). Upregulated genes belonged mainly to the interferon-γ/IRF pathway. |
| Garcia-Mazcorro, 2018. Mexico.[118] | Adults with U-CD (n = 6) vs HC (n = 12). Ultra-high throughput DNA-sequencing of ribosomal 16S. | Significantly lower abundance of Bacteroidetes ($P = 0.022$) and Fusobacteria ($P = 0.052$) in CD patients. |

Abbreviations: GFD, gluten-free diet; HC, healthy controls; T-CD, treated coeliac disease; U-CD, untreated coeliac disease.

Increased diversity over time was found in healthy controls from 4 to 6 months, which did not occur in infants who later developed CD. Differences at phylum and family level were identified, where Firmicutes, *Bifidobacterium breve* and *Enterococcus spp*. were more predominant in cases.[101] Another cohort study found no associations between microbiota at 9 and 12 months age and CD at 4 years.[102] These studies shall be regarded as preliminary given small sample sizes (10 and 9 cases, respectively) and with diverging conclusions.

Most studies of duodenal samples from individuals with untreated CD have been characterised by an increase in Bacteroidetes, Proteobacteria, Staphylococcus and Clostridiales species, and by a decrease in Bifidobacteria and Lactobacilli (Table 7). The recruitment of 'healthy' controls and treated CD patients for duodenal biopsies may introduce some bias, as endoscopies usually are performed in subjects with gastrointestinal symptoms suggestive of CD.

Differences between CD subjects and healthy controls in faecal samples tend to replicate those based on duodenal sampling (Table 8). Valuable information regarding site-specific microbiota comes from studies with dual sampling from the duodenum and faeces. As expected, lower bacterial counts and diversity were found in the duodenal sites compared to faeces, but an intra-individual correlation between the two sites regardless of case status was found.[103,104] Bacterial counts in duodenum and faeces were higher in untreated CD compared to controls.[103]

Prospective studies of the oral microbiome in CD were not identified. Cross-sectional studies of the oral microbiome have shown lower counts of oral anaerobes and higher counts of Lactobacilli in individuals with treated CD compared to healthy controls.[128,129]

The alpha-diversity of the microbiome is a frequently used measure to describe the number of different species within an individual.[130] The diversity of the duodenal and oral microbiome tended to be lower in CD.[116,129] Within genera, the duodenal diversity in CD was higher for Bifidobacteria but lower for Bacteroides and Proteobacteriae.[108,112] In faecal samples, the diversity in CD was lower for Lactobacilli and Bifidobacteria in CD compared to non-CD subjects.[125]

Genera or families of bacteria that typically are harboured in the gut in states of homoeostasis are often termed 'beneficial' and may possess antimicrobial properties against pathogens and produce bacterial metabolites with trophic functions for the gut mucosa. In contrast, 'harmful' bacteria are associated with a reduced mucosal barrier and inflammation, as reviewed elsewhere.[131] A study comparing ratios in groups of bacteria with beneficial compared to harmful properties reported lower ratios between Lacto/Bifidobacteria to Bacteroides/Enterobacteria in untreated CD and treated CD compared to healthy controls.[124]

Because groups of bacteria may have widely overlapping genome and metabolic functions, analyses of bacterial metabolites may identify functional differences across taxonomic units. Short-chain fatty acids (SCFAs) are produced by breakdown of complex fibres, and harbour anti-inflammatory properties in addition to being substrate for enterocyte growth and repair.[132] Total levels of SCFA was decreased in children with untreated CD compared to treated CD and healthy controls.[104,124] In contrast, others found total SCFAs to be higher in children with untreated CD, and normalised after more than 1 year of gluten-free diet.[133-135] There was no difference between adults with treated CD and control in fasting venous blood total SCFA was found.[136]

Because modification of the diet changes the microbiome, differences found between individuals with treated CD and healthy controls may be explained by the diet rather than the disease itself. In Table 8 some of the studies include patients who are adherent to a GFD, and findings in this group should thus be interpreted with caution. Although a subject for other reviews, it is of note that persistent symptoms on a gluten-free diet in CD patients were associated with dysbiosis.[137]

In healthy subjects, the abundance of Veillonellaceae and other bacteria mainly involved in starch metabolism was reduced in the period of GFD compared to before and after. The bacterial diversity did not change.[138] Similarly, GFD for 1 month in healthy individuals and in CD patients resulted in decreased proportions and counts of Bifidobacteria and Lactobacillae and increased counts of *E. coli* and Enterobacteriaceae.[139] A study from the US randomised children with high-risk haplotypes for CD to gluten introduction at age 4-6 or 12 months, and in repeated faecal samples found that the pattern of bacterial colonisation differed by the timing of gluten introduction.[140]

**TABLE 8** Cross-sectional studies of faecal microbiota in untreated (U-CD) and treated (T-CD) coeliac disease patients vs healthy controls (HC)

| Reference | Setting and methods | Findings |
|---|---|---|
| Faecal samples, culture-based | | |
| Collado,[119] 2007. Spain. | Children with CD (n = 26) and HC (n = 23). Culture-based method and in addition FISH using 16S rRNA probes. | The levels of Bacteroides, Clostridium and Staphylococcus were significantly higher ($P < 0.05$) in CD vs HC. The numbers of Bacteroides-Prevotella, *Cl. histolyticum*, *Eubacterium rectale*, *C. coccoides*, Atopobium, and sulphate reducing bacterial groups were also significantly higher in CD when analysed by FISH. |
| Golfetto,[120] 2014. Brazil. | Adults with T-CD (n = 14) vs HC (n = 42). | Bifidobacteria are more abundant among HC. |
| Lorenzo Pisarello,[121] 2015. Argentina. | Non-symptomatic children with T-CD vs HC. Not provided numbers. | Lactobacilli (five strains) found more frequently in HC than in T-CD. |
| Faecal samples, PCR methods | | |
| Sanz,[122] 2007. Spain. | Faecal samples from children with U-CD (n = 10) vs age-matched HC (n = 10). | No significant differences in diversity. *L. curvatus* more prevalent in U-CD, *L. casei* more prevalent in HC. Higher diversity of Bifidobacteria in HC, and more infant-type species (*B. bifidum* and *B. infantis*) in CD. |
| Sanchez,[123] 2008. Spain. | Children with U-CD (n = 10) and T-CD (n = 10) vs age-matched HC (n = 11). | Non-E.coli clones of Enterobacteriacea more common in HC than in T-CD. Group A *E. coli* more common in U-CD and T-CD, but equal distribution of *E. coli* groups in HC. Higher number of virulence genes in U-CD and T-CD vs HC. |
| Collado,[103] 2009. Spain. | Children with U-CD (n = 30), T-CD (n = 18) vs HC (n = 30). Bacterial groups quantified by real-time PCR. | Bacteroides and *Cl. leptum* groups more abundant in CD than in HC *E. coli* and Staphylococcus counts higher in U-CD than in HC, but levels were normalised on a GFD. Bifidobacterium levels lower in faeces of both groups of CD patients compared to HC. |
| DiCagno,[124] 2009. Italy. | Children with T-CD (n = 19) and HC (n = 15). PCR-denaturing gradient gel electrophoresis (DGGE) analyses by universal and group-specific primers. | Lower ratio of Lacto/Bifidobacteria to Bacteroides/Enterobacteria in U-CD and T-CD. |
| DiCagno,[104] 2011. Italy. | Children with T-CD (n = 19) vs HC (n = 15). | Higher levels of Lactobacilli, Enterococcus and Bifidobacteria in HC, higher than that of Bacteroides, Staphylococci, Salmonella/Shigella and Klebsiella in T-CD. |
| Nistal,[125] 2012. Spain. | Adults with U-CD (n = 10) and T-CD (n = 11) vs HC (n = 11). SCFA analysis in addition. | Higher *Bif. bifidus* in U-CD than in HC, lower diversity of Lactobacilli and Bifidobacteria in T-CD. SCFA lower in HC and HC on GFD. |
| Sanchez,[126] 2012. Spain. | Children with U-CD (n = 20) and T-CD (n = 20) vs age-matched HC (n = 20). | *S. epidermidis* more common in both U-CD and T-CD, *S. haemolyticus* only in U-CD compared to HC. S. aureus less abundant in U-CD than in T-CD and HC. Virulence genes lower from *S. epidermidis* in U-CD than in T-CD and HC. |
| Nobel,[127] 2018. USA. | Adult outpatients (n = 955) at a hospital including 60 with CD (no information regarding GFD). | Bacterial pathogens found more frequently in non-CD (37%) than in CD (23%). |

Abbreviations: GFD, gluten-free diet; HC, healthy controls; T-CD, treated coeliac disease; U-CD, untreated coeliac disease.

Although bacterial degradation of gluten peptides is outside the scope of this review, it is of note that in vitro[141] and in vivo studies[142,143] have characterised the ability of certain microbes to degrade gluten. These findings suggest a possible interaction between the gut microbiota and gluten peptides and may also provide fascinating possibilities for future treatment of CD.

To conclude, published data suggest that the microbiota differ between CD and healthy controls. There is insufficient evidence from human studies to infer whether this is a cause or consequence of celiac disease.

## 6 | USE OF ANTIBIOTICS AND RISK OF CD

Antibiotic exposure is among the most important perturbations influencing the composition of the early microbiome.[144] If there is a causal link from the early microbiome to CD, use of antibiotics, even by the mother during pregnancy, may be associated with subsequent risk of CD.

The two studies until date on maternal use of antibiotics during pregnancy have not found any association with the risk of CD in offspring.[35,145] In contrast, use of antibiotics during the first year of life was a significant risk factor for CD in a register-based study from Italy.[146] Similarly, in nation-wide cohorts from Denmark and Norway antibiotics during the first year of life were associated with a higher risk for CD, though attenuated in a sub-cohort for which adjustment for infections could be done.[147] Antibiotic exposure before diagnosis was associated with CD across all age categories in a Swedish register-based study.[148] These associations persisted when excluding the year before diagnosis. In contrast, no association between use of antibiotics and later CD autoimmunity was found in the TEDDY cohort with high genetic risk.[149]

The association between early antibiotics and later CD found in most studies could be due to non-causal explanations. Confounding by indication might occur, and a term used if the underlying indication for an intervention induces an artificial association. In this case, the infection prompting use of antibiotics may act as an underlying confounder. Therefore, proper adjustment for infections is important to avoid bias. If bacterial infections are increased in undetected CD, reverse causality might occur. Prospective studies limiting the antibiotic exposure to the first year of life should largely avoid this potential bias.

Health-seeking behaviour could be an underlying factor for antibiotic use and diagnostic work-up for CD, and thus confound the association. Repeated antibody screening in prospective screenings will avoid bias by detecting all cases with CD autoimmunity. In a high genetic-risk cohort, environmental risk factors may be diluted by genetic effects and should be carefully interpreted.

## 7 | POSSIBLE MECHANISMS FOR MICROBES IN CD DEVELOPMENT

Above, we have comprehensively reviewed human studies of microbes and subsequent risk of CD. A number of complex mechanisms can be involved, perhaps unique to each infectious agent. Here we briefly review some potential mechanisms, but refer interested readers to other literature for details.[150]

Even though certain infections appear to be more frequent in individuals with CD compared to controls before disease, this does not prove causality. Susceptibility to infections could be caused by genetic variants that also predispose to CD via independent pathways (pleiotropy). It has been hypothesised that genotypes predisposing to CD are prevalent in the population due to a natural selection during human evolution of genotypes that protects against infections.[151] Consistent signs of evolutionary selection for CD-associated alleles were identified for three loci linked to *IL12A*, *IL18RAP* and *SH2B3*.[151] The *SH2B3* variant risk allele for CD was found to protect against bacterial infection.[151] In a comprehensive GWAS study, SNPs within the HLA region were significantly associated with 13 common infections, some of which are associated with autoimmune diseases.[152] If the overall effect of CD predisposing genotypes is protective against infections, the observed association between infections and CD would logically be strengthened by adjusting for such genotypes.

The prevalence of CD in the affluent Finnish part of Karelia is considerably higher than in a genetically similar population in Russian Karelia.[153] Such an ecological observation has been hypothesised to be driven by differential microbiological environment. It may seem contradictory that increasing prevalence of CD occurs in parallel with lower exposure to infections if microbes are considered as potential triggers for CD. In low-endemic settings, infections peak later during a more vulnerable phase of development with potentially increased susceptibility, including reduced protection from maternal antibodies. Transfer of maternal immunity is also likely to be more prominent in populations with less hygienic living conditions, again causing a postponement of infections. Increased pathogenicity may be observed when living conditions improve, as suggested in an analogy to poliomyelitis.[154] A transition phase in socio-economic development could potentially strengthen this effect, with high maternal immunity and low exposure during infancy.

Early investigations on adenovirus 12 suggested that peptide sequences with homology to the immunogenic residues of gliadin—a molecular mimicry—could cause later T cell reactions towards gluten.[54] Though not corroborated in later studies on adenovirus, the mechanism of mimicry has also been proposed to explain an association with rotavirus infections.[41,42] Recently, homology between the short gliadin epitopes that elicit activation of T-cells and proteins from several commensal bacteria was found.[22] Particularly, gliadin reactive T-cells derived from CD patients cross-reacted with two distinct bacterial peptides, suggesting a role in CD aetiology.

A more general mechanism is that any disruption of the gut barrier by infections may allow transfer of dietary peptides resulting in stimulation of antigen-presenting cells in the submucosa (Figure 3). Gut-infecting viruses or bacteria may also cause direct lysis and cell death leading to leakage of danger signals that initiate an inflammatory process.

Inflammation increases activation of the enzyme tissue transglutaminase (tTG) in the intestine.[9] Besides having a key role in tissue repair, tTG also causes deamidation of glutamate to the negatively charged glutamic acid, a key step in the presentation of gluten peptides for T-cells.[9] Thus, the upregulation of tTG by inflammation may enhance the immunogenicity of gluten. Antibodies against tTG, the

hallmark of untreated CD, increase in some individuals transiently during infections without evidence of underlying CD.[155] After an outbreak of *Giardia lamblia*, a subset of patients with persisting symptoms had transiently elevated tTG-IgA. This returned to normal during follow-up on a gluten-containing diet in most patients, mainly in those who did not have HLA-types compatible with CD.[156]

Secretion of immunoglobulin A (IgA) constitutes a first-line defence against microbial attack in mucosal surfaces. Congenital selective IgA deficiency carries markedly increased risk for developing CD, though only a minority of CD patients are IgA deficient.[157] The HLA haplotype DQ2 which is strongly associated with CD is also in linkage disequilibrium with susceptibility haplotypes for IgA deficiency. This could well explain the association between IgA deficiency and CD, but loss of mucosal integrity due to low expression of secretory IgA could also play a role.[157,158] Interestingly, lower proportions of IgA-coated gut bacteria were found both in treated and untreated CD patients compared to healthy controls.[159]

Impairment of the regulatory T-cells ($T_{reg}$) function has been described in active CD.[160] $T_{reg}$ cells express forkhead box protein 3 ($FoxP3^+$). An alternatively spliced isoform Δ2 with lower suppressive ability compared to the full length $FoxP3^+$was increased in CD compared to healthy controls.[161] A study of cytokines produced by Th17-cells in duodenal biopsies suggests that Th17 responses to gluten and bacteria may pave the way for chronic disease with IFN-γ production by Th1 cells in the mucosa.[162] However, the role of $T_{reg}$ cells and Th17 cells in the pathogenesis CD remains to be clarified.[163]

It is unclear whether dysregulation of innate immunity plays a role in CD development. Three studies investigating toll-like receptors (TLR2, TLR4 and TLR9) as mRNA in duodenal biopsies showed heterogenous results with no clear indication that the expression differs by CD case status.[164-166] However, a differential expression by CD case status was found for genes involved in response against bacterial invasion of epithelial cells in a transcriptome analysis of duodenal biopsies.[167] The intestinal expression of naturally occurring antibacterial peptides—human β-defensins 1 (hBD1)—was markedly reduced in the duodenum of patients with active CD compared to treated CD and non-CD controls.[168-170] The downregulation of hBD1 may hypothetically precede CD and allow for bacterial proliferation. The expression was negatively correlated with the degree of villous atrophy and increased after 6 months of GFD.[169] Studies about the expression of other β-defensins in CD have shown inconsistent results.[169,170]

Animal models of gluten enteropathy have elucidated potential mechanisms, though these models are different from human CD in several important aspects.[171] Experimental infections with reovirus induced increased signalling by type I interferons. The dendritic cells may take up bystander antigen derived from food, thereby inducing Th1-responses instead of maturation of regulatory T-cells

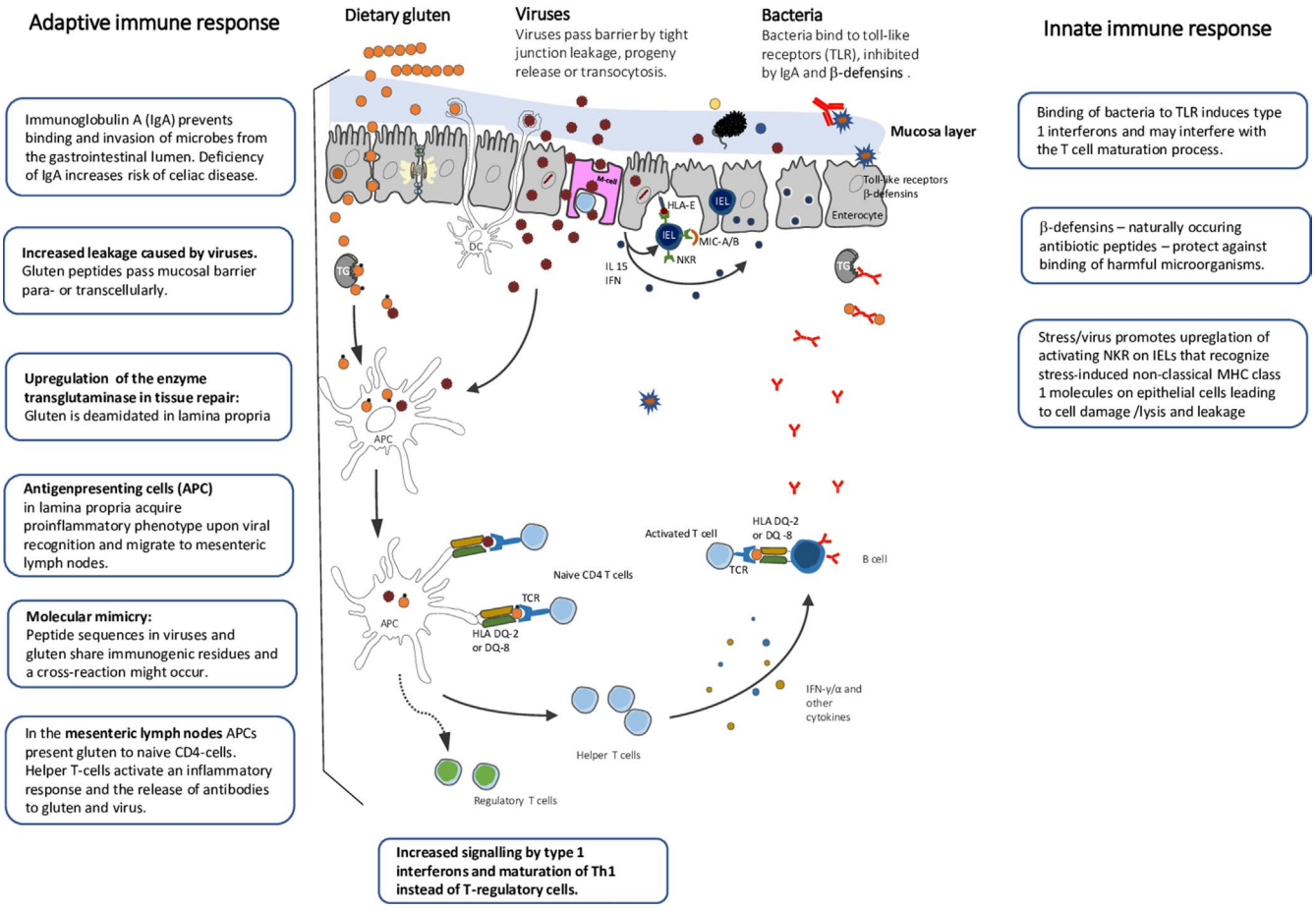


**FIGURE 3** Potential mechanisms for how microbiota may influence the pathological process of coeliac disease

(Figure 3).[20] Dendritic cells present the peptides for T-cells, and B-cells have also been shown to act as antigen-presenting cells.[172] Interestingly, infections with rotavirus cause massive B-cell expansion. This could potentially increase antigen presentation, expansion of reactive T-cells and trigger T-cell-mediated damage typical of CD.[173] A murine Norovirus strain has also been shown to induce Th1 inflammatory responses to dietary antigens in an animal model.[21]

A transgenic DQ8 mouse model was utilised to study the response to gluten in three groups differing by microbiome: germ-free, clean specific pathogen-free (SPF, strictly monitored for the absence of a variety of pathobionts or Proteobacteria) or conventional SPF. Conventional SPF mice had increased responses to gluten, while in clean SPF mice the protection against gluten-induced pathology was reversed by infection with Proteobacteria.[174] If this experimental model allows translation to human biology, it demonstrates how the microbiome potentially modulates the response to gluten.

## 8 | DISCUSSION

In this review, we aimed to capture all published human studies investigating microbes in association with risk of CD, and hence potentially influencing the aetiological pathways in CD. However, some studies may have been left undetected in our literature search. A more likely threat towards validity of the findings is, however, a publication bias, as studies reporting negative associations are less likely to be submitted and accepted for publication. The studies included in the present review showed great diversity in methodology and design, hampering the possibility to perform meaningful pooled measures of association. This heterogeneity pertains to time periods of infections, methods to measure and detect infections and the variety of microbes studied. The statistical power of the prospective studies was generally low, though methodologically superior to cross-sectional studies.

Studying infections as potential triggers in CD is complicated by the potentially long lag time from exposure to diagnosis (Figure 1).[25] Collection of repeated samples from each participant allows for the study of temporal associations, as compared to single assessments of the exposure. Viruses present at diagnosis may have infected during this lag time after seroconversion, and consequently be unrelated to the disease aetiology. In contrast, infections that contributed to the disease process may have been cleared at diagnosis, as a "hit-and-run"-type mechanism may have been involved.[175]

Furthermore, to study whether microbial colonisation vs clinical disease differ in their association with subsequent CD, repeated sampling in longitudinal studies provide unique opportunities. For example, a recent study suggested that a stool sample positive for enterovirus concomitant with symptoms was strongly associated with subsequent CD than PCR positivity regardless of symptoms.[49] Obviously the challenge remains to robustly and validly distinguish between colonisation and clinical disease.

## 9 | CONCLUSIONS AND FUTURE RESEARCH

Our review points to several microbes potentially being linked to CD. Observational studies have inherent limitations to prove causality, and most of the studies available for the current review are of cross-sectional design and consequently risk of reverse causation. In the chain of events where gluten and genes are ubiquitous a missing link is likely to involve microbial factors, though clearly well-designed prospective studies are required.

Corroboration of findings from observational studies in vitro has now become more feasible with novel techniques under controlled settings using live human cell cultures as organoids/enteroids and "CD on a chip".[13,176] Translation to human medicine remains a challenge, as these models do not have the complex immune system of the gut mucosa. Whether certain microbes could induce loss of gluten tolerance, and potential mechanisms for such an effect, should be further investigated in human and animal studies.

Interventional studies are required to further strengthen the evidence and translate basic science to public health interventions: Vaccines against rotavirus and potentially other viruses should be further studied with CD as specific endpoint. Probiotics either in primary prophylaxis or given to asymptomatic individuals with CD antibodies are being explored.[177,178] Prevention studies of CD require sufficient resources and time, and need to be based on the best available evidence from basic science and human observational studies.

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### AUTHORSHIP

*Guarantor of the article*: Ketil Størdal.

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### ORCID

*Ketil Størdal* https://orcid.org/0000-0001-7826-8646
*Kalle Kurppa* https://orcid.org/0000-0003-4757-2164

### REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013;62:43-52.
2. Rubio–Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology*. 2009;137:88-93.
3. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther*. 2007;26:1217-1225.

4. Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. *Ann Med*. 2010;42:530-538.
5. Gutierrez-Achury J, Zhernakova A, Pulit SL, et al. Fine mapping in the MHC region accounts for 18% additional genetic risk for celiac disease. *Nat Genet*. 2015;47:577-578.
6. Izzo V, Pinelli M, Tinto N, et al. Improving the estimation of celiac disease sibling risk by non-HLA genes. *PLoS One*. 2011;6:e26920.
7. Kuja-Halkola R, Lebwohl B, Halfvarson J, Wijmenga C, Magnusson PK, Ludvigsson JF. Heritability of non-HLA genetics in coeliac disease: a population-based study in 107 000 twins. *Gut*. 2016;65:1793-1798.
8. Bjorck S, Brundin C, Lorinc E, Lynch KF, Agardh D. Screening detects a high proportion of celiac disease in young HLA-genotyped children. *J Pediatr Gastroenterol Nutr*. 2010;50:49-53.
9. Molberg Ø, Mcadam SN, Körner R, et al. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. *Nat Med*. 1998;4:713-717.
10. Abadie V, Sollid LM, Barreiro LB, Jabri B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu Rev Immunol*. 2011;29:493-525.
11. Romanos J, Rosén A, Kumar V, et al. Improving coeliac disease risk prediction by testing non-HLA variants additional to HLA variants. *Gut*. 2014;63:415-422.
12. Dubois PCA, Trynka G, Franke L, et al. Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet*. 2010;42:295-302.
13. Moerkens R, Mooiweer J, Withoff S, Wijmenga C. Celiac disease-on-chip: modeling a multifactorial disease in vitro. *United European Gastroenterol J*. 2019;7:467-476.
14. Szajewska H, Shamir R, Chmielewska A, et al. Systematic review with meta-analysis: early infant feeding and coeliac disease–update 2015. *Aliment Pharmacol Ther*. 2015;41:1038-1054.
15. Andrén Aronsson C, Lee H-S, Hård af Segerstad EM, et al. Association of gluten intake during the first 5 years of life with incidence of celiac disease autoimmunity and celiac disease among children at increased risk. *JAMA*. 2019;322:514-523.
16. Lund-Blix NA, Marild K, Tapia G, Norris JM, Stene LC, Stordal K. Gluten intake in early childhood and risk of celiac disease in childhood: a nationwide cohort study. *Am J Gastroenterol*. 2019;114:1299-1306.
17. Hills RD Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut microbiome: profound implications for diet and disease. *Nutrients*. 2019;11:1613.
18. Erickson AK, Jesudhasan PR, Mayer MJ, Narbad A, Winter SE, Pfeiffer JK. Bacteria facilitate enteric virus co-infection of mammalian cells and promote genetic recombination. *Cell Host Microbe*. 2018;23:77-88 e75.
19. Robinson CM, Jesudhasan PR, Pfeiffer JK. Bacterial lipopolysaccharide binding enhances virion stability and promotes environmental fitness of an enteric virus. *Cell Host Microbe*. 2014;15:36-46.
20. Bouziat R, Hinterleitner R, Brown JJ, et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science (New York, NY)*. 2017;356:44-50.
21. Bouziat R, Biering SB, Kouame E, et al. Murine norovirus infection induces TH1 inflammatory responses to dietary antigens. *Cell Host Microbe*. 2018;24:677-688.e675.
22. Petersen J, Ciacchi L, Tran MT, et al. T cell receptor cross-reactivity between gliadin and bacterial peptides in celiac disease. *Nat Struct Mol Biol*. 2020;27:49-61.
23. Simell S, Hoppu S, Simell T, et al. Age at development of type 1 diabetes- and celiac disease-associated antibodies and clinical disease in genetically susceptible children observed from birth. *Diabetes Care*. 2010;33:774-779.
24. Crespo Escobar P, Castillejo G, Martínez-Ojinaga E, et al. Ten years of follow-up of the Spanish cohort of the European PreventCD study: the lessons learned. *Rev Esp Enferm Dig*. 2018;110:493-499.
25. Simell S, Kupila A, Hoppu S, et al. Natural history of transglutaminase autoantibodies and mucosal changes in children carrying HLA-conferred celiac disease susceptibility. *Scand J Gastroenterol*. 2005;40:1182-1191.
26. Sandberg-Bennich S, Dahlquist G, Källén B. Coeliac disease is associated with intrauterine growth and neonatal infections. *Acta Paediatr*. 2002;91:30-33.
27. Welander A, Tjernberg AR, Montgomery SM, Ludvigsson J, Ludvigsson JF. Infectious disease and risk of later celiac disease in childhood. *Pediatrics*. 2010;125:e530-e536.
28. Marild K, Kahrs CR, Tapia G, Stene LC, Stordal K. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *Am J Gastroenterol*. 2015;110:1475-1484.
29. Beyerlein A, Donnachie E, Ziegler AG. Infections in early life and development of celiac disease. *Am J Epidemiol*. 2017;186:1277-1280.
30. Simre K, Uibo O, Peet A, et al. Exploring the risk factors for differences in the cumulative incidence of coeliac disease in two neighboring countries: the prospective DIABIMMUNE study. *Dig Liver Dis*. 2016;48:1296-1301.
31. 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.e695.
32. 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.
33. Saalman R, Fällström SP. High incidence of urinary tract infection in patients with coeliac disease. *Arch Dis Child*. 1996;74:170-171.
34. Bittker SS, Bell KR. Potential risk factors for celiac disease in childhood: a case-control epidemiological survey. *Clin Exp Gastroenterol*. 2019;12:303-319.
35. Mårild K, Kahrs CR, Tapia G, Stene LC, Størdal K. Maternal infections, antibiotics, and paracetamol in pregnancy and offspring celiac disease: a cohort study. *J Pediatr Gastroenterol Nutr*. 2017;64:730-736.
36. Olén O, Montgomery SM, Ekbom A, Bollgren I, Ludvigsson JF. Urinary tract infections in pregnant women with coeliac disease. *Scand J Gastroenterol*. 2007;42:186-193.
37. Riddle MS, Murray JA, Porter CK. The incidence and risk of celiac disease in a healthy US adult population. *Am J Gastroenterol*. 2012;107:1248-1255.
38. Riddle MS, Murray JA, Cash BD, Pimentel M, Porter CK. Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study. *Dig Dis Sci*. 2013;58:3242-3245.
39. Stordal K, Lundeby KM, Brantsaeter AL, et al. Breastfeeding and infant hospitalisation for infections: large cohort- and sibling analysis. *J Pediatr Gastroenterol Nutr*. 2017;65:225-231.
40. 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;101:2333-2340.
41. Zanoni G, Navone R, Lunardi C, et al. In celiac disease, a subset of autoantibodies against transglutaminase binds toll-like receptor 4 and induces activation of monocytes. *PLoS Medicine*. 2006;3:e358.
42. 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;56:465-476.
43. Ziberna F, De Lorenzo G, Schiavon V, et al. Lack of evidence of rotavirus-dependent molecular mimicry as a trigger of coeliac disease. *Clin Exp Immunol*. 2016;186:356-363.

44. Hemming-Harlo M, Lahdeaho ML, Maki M, Vesikari T. Rotavirus vaccination does not increase type 1 diabetes and may decrease celiac disease in children and adolescents. *Pediatr Infect Dis J*. 2019;38:539-541.
45. Vaarala O, Jokinen J, Lahdenkari M, Leino T. Rotavirus vaccination and the risk of celiac disease or type 1 diabetes in Finnish children at early life. *Pediatr Infect Dis J*. 2017;36:674-675.
46. Mercalli A, Lampasona V, Klingel K, et al. No evidence of enteroviruses in the intestine of patients with type 1 diabetes. *Diabetologia*. 2012;55:2479-2488.
47. Oikarinen M, Tauriainen S, Oikarinen S, et al. Type 1 diabetes is associated with enterovirus infection in gut mucosa. *Diabetes*. 2012;61:687-691.
48. Simre K, Uibo O, Peet A, et al. Early-life exposure to common virus infections did not differ between coeliac disease patients and controls. *Acta Paediatr*. 2019;108:1709-1716.
49. 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.
50. 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;69:1416-1422.
51. Carlsson AK, Lindberg BA, Bredberg AC, Hyöty H, Ivarsson SA. Enterovirus infection during pregnancy is not a risk factor for celiac disease in the offspring. *J Pediatr Gastroenterol Nutr*. 2002;35:649-652.
52. Tapia G, Chudá K, Kahrs CR, et al. Parechovirus infection in early childhood and association with subsequent celiac disease. 2020:2020.2004.2028.20082024.
53. Kagnoff MF. Coeliac disease: genetic, immunological and environmental factors in disease pathogenesis. *Scand J Gastroenterol Suppl*. 1985;114:45-54.
54. Kagnoff MF, Austin RK, Hubert JJ, Bernardin JE, Kasarda DD. Possible role for a human adenovirus in the pathogenesis of celiac disease. *J Exp Med*. 1984;160:1544-1557.
55. 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.
56. Howdle PD, Blair Zajdel ME, Smart CJ, Trejdosiewicz LK, Blair GE, Losowky MS. Lack of a serologic response to an E1B protein of adenovirus 12 in coeliac disease. *Scand J Gastroenterol*. 1989;24:282-286.
57. Lähdeaho ML, Lehtinen M, Rissa HR, Hyöty H, Reunala T, Mäki M. Antipeptide antibodies to adenovirus E1b protein indicate enhanced risk of celiac disease and dermatitis herpetiformis. *Int Arch Allergy Immunol*. 1993;101:272-276.
58. Carter MJ, Willcocks MM, Mitchison HC, Record CO, Madeley CR. Is a persistent adenovirus infection involved in coeliac disease? *Gut*. 1989;30:1563-1567.
59. Mahon J, Blair GE, Wood GM, Scott BB, Losowsky MS, Howdle PD. Is persistent adenovirus 12 infection involved in coeliac disease? A search for viral DNA using the polymerase chain reaction. *Gut*. 1991;32:1114-1116.
60. Vesy CJ, Greenson JK, Papp AC, Snyder PJ, Qualman SJ, Prior TW. Evaluation of celiac disease biopsies for adenovirus 12 DNA using a multiplex polymerase chain reaction. *Mod Path*. 1993;6:61-64.
61. Lawler M, Humphries P, O'Farrelly C, et al. Adenovirus 12 E1A gene detection by polymerase chain reaction in both the normal and coeliac duodenum. *Gut*. 1994;35:1226-1232.
62. Tjernberg AR, Ludvigsson JF. Children with celiac disease are more likely to have attended hospital for prior respiratory syncytial virus infection. *Dig Dis Sci*. 2014;59:1502-1508.
63. Kårhus LL, Gunnes N, Størdal K, et al. Influenza and risk of later celiac disease: a cohort study of 2.6 million people. *Scand J Gastroenterol*. 2018;53:15-23.
64. Ruggeri C, La Masa AT, Rudi S, et al. Celiac disease and non-organ-specific autoantibodies in patients with chronic hepatitis C virus infection. *Dig Dis Sci*. 2008;53:2151-2155.
65. Fine KD, Ogunji F, Saloum Y, Beharry S, Crippin J, Weinstein J. Celiac sprue: another autoimmune syndrome associated with hepatitis C. *Am J Gastroenterol*. 2001;96:138-145.
66. Hernandez L, Johnson TC, Naiyer AJ, et al. Chronic hepatitis C virus and celiac disease, is there an association? *Dig Dis Sci*. 2008;53:256-261.
67. Thevenot T, Denis J, Jouannaud V, et al. Coeliac disease in chronic hepatitis C: a French multicentre prospective study. *Aliment Pharmacol Ther*. 2007;26:1209-1216.
68. Vivas S, Ruiz de Morales JM, Martinez J, et al. Human recombinant anti-transglutaminase antibody testing is useful in the diagnosis of silent coeliac disease in a selected group of at-risk patients. *Eur J Gastro Hepatol*. 2003;15:479-483.
69. Gravina AG, Federico A, Masarone M, et al. Coeliac disease and C virus-related chronic hepatitis: a non association. *BMC Res Notes*. 2012;5:533.
70. Sjomina O, Pavlova J, Niv Y, Leja M. Epidemiology of *Helicobacter pylori* infection. *Helicobacter*. 2018;23:e12514.
71. Diamanti A, Maino C, Niveloni S, et al. Characterization of gastric mucosal lesions in patients with celiac disease: a prospective controlled study. *Am J Gastroenterol*. 1999;94:1313-1319.
72. Ciacci C, Squillante A, Rendina D, et al. *Helicobacter pylori* infection and peptic disease in coeliac disease. *Eur J Gastro Hepatol*. 2000;12:1283-1287.
73. Aydogdu S, Cakir M, Yuksekkaya HA, et al. *Helicobacter pylori* infection in children with celiac disease. *Scand J Gastroenterol*. 2008;43:1088-1093.
74. Lebwohl B, Blaser MJ, Ludvigsson JF, et al. Decreased risk of celiac disease in patients with *Helicobacter pylori* colonization. *Am J Epidemiol*. 2013;178:1721-1730.
75. Lasa J, Zubiaurre I, Dima G, Peralta D, Soifer L *HELICOBACTER PYLORI* PREVALENCE IN PATIENTS WITH CELIAC DISEASE: results from a cross-sectional study. *Arq Gastroenterol*. 2015;52:139-142.
76. Simondi D, Ribaldone DG, Bonagura GA, et al. *Helicobacter pylori* in celiac disease and in duodenal intraepithelial lymphocytosis: active protagonist or innocent bystander? *Clin Res Hepatol Gastroenterol*. 2015;39:740-745.
77. Uyanikoglu A, Dursun H, Yenice N. Is there any association between celiac disease and *Helicobacter pylori*? *Euroasian J Hepatogastroenterol*. 2016;6:103-105.
78. Narang M, Puri AS, Sachdeva S, Singh J, Kumar A, Saran RK. Celiac disease and *Helicobacter pylori* infection in children: is there any association? *J Gastroenterol Hepatol*. 2017;32:1178-1182.
79. Lucero Y, Oyarzún A, O'Ryan M, et al. *Helicobacter pylori* cagA+ is associated with milder duodenal histological changes in Chilean celiac patients. *Front Cell Infect Microbiol*. 2017;7:376.
80. Agin M, Batun I, Ozdemir S, Doran F, Tumgor G. Prevalence of *Helicobacter pylori* in Turkish children with celiac disease and its effect on clinical, histopathological, and laboratory parameters. *Arch Med Sci*. 2019;15:1475-1481.
81. Crabtree JE, O'Mahony S, Wyatt JI, et al. *Helicobacter pylori* serology in patients with coeliac disease and dermatitis herpetiformis. *J Clin Pathol*. 1992;45:597-600.
82. Luzza F, Mancuso M, Imeneo M, et al. *Helicobacter pylori* infection in children with celiac disease: prevalence and clinicopathologic features. *J Pediatr Gastroenterol Nutr*. 1999;28:143-146.
83. Konturek PC, Karczewska E, Dieterich W, Hahn EG, Schuppan D. Increased prevalence of *Helicobacter pylori* infection in patients with celiac disease. *Am J Gastroenterol*. 2000;95:3682-3683.
84. Jozefczuk J, Bancerz B, Walkowiak M, et al. Prevalence of *Helicobacter pylori* infection in pediatric celiac disease. *Eur Rev Med Pharmacol Sci*. 2015;19:2031-2035.

85. Bartels LE, Jepsen P, Christensen LA, Gerdes LU, Vilstrup H, Dahlerup JF. Diagnosis of *Helicobacter pylori* infection is associated with lower prevalence and subsequent incidence of Crohn's disease. *J Crohns Colitis*. 2016;10:443-448.
86. Dore MP, Salis R, Loria MF, Villanacci V, Bassotti G, Pes GM. *Helicobacter pylori* infection and occurrence of celiac disease in subjects HLA-DQ2/DQ8 positive: a prospective study. *Helicobacter*. 2018;23:e12465.
87. Jansen MAE, van den Heuvel D, van der Zwet KVM, et al. Herpesvirus infections and transglutaminase type 2 antibody positivity in childhood: the generation R study. *J Pediatr Gastroenterol Nutr*. 2016;63:423-430.
88. Plot L, Amital H, Barzilai O, et al. Infections may have a protective role in the etiopathogenesis of celiac disease. *Ann N Y Acad Sci*. 2009;1173:670-674.
89. Viskari H, Paronen J, Keskinen P, et al. Humoral beta-cell autoimmunity is rare in patients with the congenital rubella syndrome. *Clin Exp Immunol*. 2003;133:378-383.
90. Alaedini A, Lebwohl B, Wormser GP, Green PH, Ludvigsson JF. Borrelia infection and risk of celiac disease. *BMC Med*. 2017;15:169.
91. Ashorn S, Raukola H, Välineva T, et al. Elevated serum anti-*Saccharomyces* cerevisiae, anti-I2 and anti-OmpW antibody levels in patients with suspicion of celiac disease. *J Clin Immunol*. 2008;28:486-494.
92. Biet F, Gendt L, Anton E, Ballot E, Hugot JP, Johanet C. Serum antibodies to *Mycobacterium avium* subspecies *paratuberculosis* combined with anti-*Saccharomyces* cerevisiae antibodies in Crohn's disease patients: prevalence and diagnostic role. *Dig Dis Sci*. 2011;56:1794-1800.
93. Verdier J, Deroche L, Allez M, et al. Specific IgG response against *Mycobacterium avium paratuberculosis* in children and adults with Crohn's disease. *PLoS One*. 2013;8:e62780.
94. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299:1259-1260.
95. McSorley HJ, Gaze S, Daveson J, et al. Suppression of inflammatory immune responses in celiac disease by experimental hookworm infection. *PLoS One*. 2011;6:e24092.
96. Giacomin P, Zakrzewski M, Croese J, et al. Experimental hookworm infection and escalating gluten challenges are associated with increased microbial richness in celiac subjects. *Sci Rep*. 2015;5:13797.
97. Giacomin P, Zakrzewski M, Jenkins TP, et al. Changes in duodenal tissue-associated microbiota following hookworm infection and consecutive gluten challenges in humans with coeliac disease. *Sci Rep*. 2016;6:36797.
98. Daveson AJ, Jones DM, Gaze S, et al. Effect of hookworm infection on wheat challenge in celiac disease–a randomised double-blinded placebo controlled trial. *PLoS One*. 2011;6:e17366.
99. Croese J, Giacomin P, Navarro S, et al. Experimental hookworm infection and gluten microchallenge promote tolerance in celiac disease. *J Allergy Clin Immunol*. 2015;135:508-516.
100. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486:222-227.
101. Olivares M, Walker AW, Capilla A, et al. Gut microbiota trajectory in early life may predict development of celiac disease. *Microbiome*. 2018;6:36.
102. Rintala A, Riikonen I, Toivonen A, et al. Early fecal microbiota composition in children who later develop celiac disease and associated autoimmunity. *Scand J Gastroenterol*. 2018;53:403-409.
103. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *J Clin Pathol*. 2009;62:264-269.
104. Di Cagno R, De Angelis M, De Pasquale I, et al. Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. *BMC Microbiol*. 2011;11:219.
105. Forsberg G, Fahlgren A, Hörstedt P, Hammarström S, Hernell O, Hammarström ML. Presence of bacteria and innate immunity of intestinal epithelium in childhood celiac disease. *Am J Gastroenterol*. 2004;99:894-904.
106. Nadal I, Donat E, Donant E, Ribes-Koninckx C, Calabuig M, Sanz Y. Imbalance in the composition of the duodenal microbiota of children with coeliac disease. *J Med Microbiol*. 2007;56:1669-1674.
107. Ou G, Hedberg M, Hörstedt P, et al. Proximal small intestinal microbiota and identification of rod-shaped bacteria associated with childhood celiac disease. *Am J Gastroenterol*. 2009;104:3058-3067.
108. Sánchez E, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Intestinal Bacteroides species associated with coeliac disease. *J Clin Pathol*. 2010;63:1105-1111.
109. Schippa S, Iebba V, Barbato M, et al. A distinctive 'microbial signature' in celiac pediatric patients. *BMC Microbiol*. 2010;10:175.
110. Nistal E, Caminero A, Herrán AR, et al. Differences of small intestinal bacteria populations in adults and children with/without celiac disease: effect of age, gluten diet, and disease. *Inflamm Bowel Dis*. 2012;18:649-656.
111. Cheng J, Kalliomäki M, Heilig HG, et al. Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease. *BMC Gastroenterol*. 2013;13:113.
112. 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;19:934-941.
113. Sánchez E, Donat E, Ribes-Koninckx C, Fernández-Murga ML, Sanz Y. Duodenal-mucosal bacteria associated with celiac disease in children. *Appl Environ Microbiol*. 2013;79:5472-5479.
114. D'Argenio V, Casaburi G, Precone V, et al. Metagenomics reveals dysbiosis and a potentially pathogenic *N. flavescens* strain in duodenum of adult celiac patients. *Am J Gastroenterol*. 2016;111:879-890.
115. de Meij TG, Budding AE, Grasman ME, Kneepkens CM, Savelkoul PH, Mearin ML. Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease. *Scand J Gastroenterol*. 2013;48:530-536.
116. 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;120:1691-1700.
117. Pietz G, De R, Hedberg M, et al. Immunopathology of childhood celiac disease-Key role of intestinal epithelial cells. *PLoS One*. 2017;12:e0185025.
118. Garcia-Mazcorro J, Rivera-Gutierrez X, Cobos-Quevedo O, et al. First insights into the gut microbiota of Mexican patients with celiac disease and non-celiac gluten sensitivity. *Nutrients*. 2018;10:1641.
119. Collado MC, Calabuig M, Sanz Y. Differences between the fecal microbiota of coeliac infants and healthy controls. *Curr Issues Intest Microbiol*. 2007;8:9-14.
120. Golfetto L, de Senna FD, Hermes J, Beserra BT, França Fda S, Martinello F. Lower bifidobacteria counts in adult patients with celiac disease on a gluten-free diet. *Arq Gastroenterol*. 2014;51:139-143.
121. Lorenzo Pisarello MJ, Vintiñi EO, González SN, Pagani F, Medina MS. Decrease in lactobacilli in the intestinal microbiota of celiac children with a gluten-free diet, and selection of potentially probiotic strains. *Can J Microbiol*. 2015;61:32-37.
122. Sanz Y, Sánchez E, Marzotto M, Calabuig M, Torriani S, Dellaglio F. Differences in faecal bacterial communities in coeliac and healthy children as detected by PCR and denaturing gradient gel electrophoresis. *FEMS Immunol Med Microbiol*. 2007;51:562-568.

123. Sánchez E, Nadal I, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Reduced diversity and increased virulence-gene carriage in intestinal enterobacteria of coeliac children. *BMC Gastroenterol*. 2008;8:50.
124. 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;75:3963-3971.
125. Nistal E, Caminero A, Vivas S, et al. Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients. *Biochimie*. 2012;94:1724-1729.
126. Sánchez E, Ribes-Koninckx C, Calabuig M, Sanz Y. Intestinal Staphylococcus spp. and virulent features associated with coeliac disease. *J Clin Pathol*. 2012;65:830-834.
127. Nobel YR, Axelrad J, Lewis SK, et al. Stool PCR for gastrointestinal pathogens in patients with and without immune-mediated intestinal diseases. *Dig Dis Sci*. 2018;63:996-1002.
128. Acar S, Yetkiner AA, Ersin N, Oncag O, Aydogdu S, Arikan C. Oral findings and salivary parameters in children with celiac disease: a preliminary study. *Med Princ Pract*. 2012;21:129-133.
129. Tian NA, Faller L, Leffler DA, et al. Salivary gluten degradation and oral microbial profiles in healthy individuals and celiac disease patients. *Appl Environ Microbiol*. 2017;83:e03330.
130. Hill TC, Walsh KA, Harris JA, Moffett BF. Using ecological diversity measures with bacterial communities. *FEMS Microbiol Ecol*. 2003;43:1-11.
131. Iacob S, Iacob DG. Infectious threats, the intestinal barrier, and its trojan horse: dysbiosis. *Front Microbiol*. 2019;10:1676.
132. Gill PA, van Zelm MC, Muir JG, Gibson PR. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. *Aliment Pharmacol Ther*. 2018;48:15-34.
133. Tjellstrom B, Stenhammar L, Hogberg L, et al. Gut microflora associated characteristics in children with celiac disease. *Am J Gastroenterol*. 2005;100:2784-2788.
134. Tjellström BO, Stenhammar L, Högberg L, et al. Screening-detected and symptomatic untreated celiac children show similar gut microflora-associated characteristics. *Scand J Gastroenterol*. 2010;45:1059-1062.
135. Tjellström BO, Högberg L, Stenhammar L, et al. Faecal short-chain fatty acid pattern in childhood coeliac disease is normalised after more than one year's gluten-free diet. *Microb Ecol Health Dis*. 2013;24:20905.
136. Jakobsdottir G, Bjerregaard JH, Skovbjerg H, Nyman M. Fasting serum concentration of short-chain fatty acids in subjects with microscopic colitis and celiac disease: no difference compared with controls, but between genders. *Scand J Gastroenterol*. 2013;48:696-701.
137. Wacklin P, Laurikka P, Lindfors K, et al. Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. *Am J Gastroenterol*. 2014;109:1933-1941.
138. Bonder MJ, Tigchelaar EF, Cai X, et al. The influence of a short-term gluten-free diet on the human gut microbiome. *Genome Med*. 2016;8:45.
139. De Palma G, Nadal I, Collado MC, Sanz Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br J Nutr*. 2009;102:1154-1160.
140. 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.
141. Caminero A, Herrán AR, Nistal E, et al. Diversity of the cultivable human gut microbiome involved in gluten metabolism: isolation of microorganisms with potential interest for coeliac disease. *FEMS Microbiol Ecol*. 2014;88:309-319.
142. Zamakhchari M, Wei G, Dewhirst F, et al. Identification of Rothia bacteria as gluten-degrading natural colonizers of the upper gastro-intestinal tract. *PLoS One*. 2011;6:e24455.
143. Fernandez-Feo M, Wei G, Blumenkranz G, et al. The cultivable human oral gluten-degrading microbiome and its potential implications in coeliac disease and gluten sensitivity. *Clin Microbiol Infect*. 2013;19:E386-E394.
144. Yassour M, Vatanen T, Siljander H, et al. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med*. 2016;8:343ra81.
145. Mårild K, Ludvigsson J, Sanz Y, Ludvigsson JF. Antibiotic exposure in pregnancy and risk of coeliac disease in offspring: a cohort study. *BMC Gastroenterol*. 2014;14:75.
146. 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.
147. Dydensborg Sander S, Nybo Andersen AM, Murray JA, Karlstad Ø, Husby S, Størdal K. Association between antibiotics in the first year of life and celiac disease. *Gastroenterology*. 2019;156:2217-2229.
148. 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.
149. Kemppainen KM, Vehik K, Lynch KF, et al. Association between early-life antibiotic use and the risk of islet or celiac disease autoimmunity. *JAMA Pediatr*. 2017;171:1217-1225.
150. Verdu EF, Galipeau HJ, Jabri B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2015;12:497-506.
151. Zhernakova A, Elbers CC, Ferwerda B, et al. Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection. *Am J Hum Genet*. 2010;86:970-977.
152. Tian C, Hromatka BS, Kiefer AK, et al. Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections. *Nat Commun*. 2017;8:599.
153. Kondrashova A, Mustalahti K, Kaukinen K, et al. Lower economic status and inferior hygienic environment may protect against celiac disease. *Ann Med*. 2008;40:223-231.
154. Gamble DR. The epidemiology of insulin dependent diabetes with particular reference to the relationship of virus infection to its etiology. *Epidemiol Rev*. 1980;2:49-70.
155. Ferrara F, Quaglia S, Caputo I, et al. Anti-transglutaminase antibodies in non-coeliac children suffering from infectious diseases. *Clin Exp Immunol*. 2010;159:217-223.
156. Hanevik K, Wik E, Langeland N, Hausken T. Transient elevation of anti-transglutaminase and anti-endomysium antibodies in Giardia infection. *Scand J Gastroenterol*. 2018;53:809-812.
157. Odineal DD, Gershwin ME. The epidemiology and clinical manifestations of autoimmunity in selective IgA deficiency. *Clin Rev Allergy Immunol*. 2020;58:107-133.
158. Wang N, Hammarstrom L. IgA deficiency: what is new? *Curr Opin Allergy Clin Immunol*. 2012;12:602-608.
159. De Palma G, Nadal I, Medina M, et al. Intestinal dysbiosis and reduced immunoglobulin-coated bacteria associated with coeliac disease in children. *BMC Microbiol*. 2010;10:63.
160. Di Sabatino A, Lenti MV, Giuffrida P, Vanoli A, Corazza GR. New insights into immune mechanisms underlying autoimmune diseases of the gastrointestinal tract. *Autoimmun Rev*. 2015;14:1161-1169.
161. Serena G, Yan S, Camhi S, et al. Proinflammatory cytokine interferon-γ and microbiome-derived metabolites dictate epigenetic

switch between forkhead box protein 3 isoforms in coeliac disease. *Clin Exp Immunol*. 2017;187:490-506.
162. Sjöberg V, Sandström O, Hedberg M, Hammarström S, Hernell O, Hammarström ML. Intestinal T-cell responses in celiac disease - impact of celiac disease associated bacteria. *PLoS One*. 2013;8:e53414.
163. Mazzarella G. Effector and suppressor T cells in celiac disease. *World J Gastroenterol*. 2015;21:7349-7356.
164. 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;54:727-732.
165. Ghasiyari H, Rostami-Nejad M, Amani D, et al. Diverse profiles of Toll-like receptors 2, 4, 7, and 9 mRNA in peripheral blood and biopsy specimens of patients with celiac disease. *J Immunol Res*. 2018;2018:7587095.
166. Eiró N, González-Reyes S, González L, et al. Duodenal expression of Toll-like receptors and interleukins are increased in both children and adult celiac patients. *Dig Dis Sci*. 2012;57:2278-2285.
167. Bragde H, Jansson U, Fredrikson M, Grodzinsky E, Söderman J. Celiac disease biomarkers identified by transcriptome analysis of small intestinal biopsies. *Cell Mol Life Sci*. 2018;75:4385-4401.
168. Intrieri M, Rinaldi A, Scudiero O, Autiero G, Castaldo G, Nardone G. Low expression of human beta-defensin 1 in duodenum of celiac patients is partially restored by a gluten-free diet. *Clin Chem Lab Med*. 2010;48:489-492.
169. Taha AS, Faccenda E, Angerson WJ, Balsitis M, Kelly RW. Natural antibiotic expression in celiac disease–correlation with villous atrophy and response to a gluten-free diet. *Dig Dis Sci*. 2005;50:791-795.
170. Vordenbäumen S, Pilic D, Otte JM, Schmitz F, Schmidt-Choudhury A. Defensin-mRNA expression in the upper gastrointestinal tract is modulated in children with celiac disease and *Helicobacter pylori*-positive gastritis. *J Pediatr Gastroenterol Nutr*. 2010;50:596-600.
171. Ju JM, Marietta EV, Murray JA. Generating transgenic mouse models for studying celiac disease. *Methods Mol Biol*. 2015;1326:23-33.
172. Stamnaes J, Sollid LM. Celiac disease: autoimmunity in response to food antigen. *Semin Immunol*. 2015;27:343-352.
173. Deal EM, Lahl K, Narvaez CF, Butcher EC, Greenberg HB. Plasmacytoid dendritic cells promote rotavirus-induced human and murine B cell responses. *J Clin Invest*. 2013;123:2464-2474.
174. Galipeau HJ, McCarville JL, Huebener S, et al. Intestinal microbiota modulates gluten-induced immunopathology in humanized mice. *Am J Pathol*. 2015;185:2969-2982.
175. Stene LC, Rewers M. Immunology in the clinic review series; focus on type 1 diabetes and viruses: the enterovirus link to type 1 diabetes: critical review of human studies. *Clin Exp Immunol*. 2012;168:12-23.
176. George MM, Rahman M, Connors J, Stadnyk AW. Opinion: are organoids the end of model evolution for studying host intestinal epithelium/microbe interactions? *Microorganisms*. 2019;7:406.
177. Hakansson A, Andren Aronsson C, Brundin C, Oscarsson E, Molin G, Agardh D. 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.
178. Tye-Din JA, Galipeau HJ, Agardh D. Celiac disease: a review of current concepts in pathogenesis, prevention, and novel therapies. *Front Pediatr*. 2018;6:350.

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