nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-024-01032-w

Review article

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Coeliac disease: complications and comorbidities

Jonas F. Ludvigsson[1,2,3] ✉, Jialu Yao[1], Benjamin Lebwohl[2,4], Peter H. R. Green[2], Shuai Yuan[5] & Daniel A. Leffler[6,7]

Abstract

Coeliac disease is an autoimmune disease characterized by small intestinal villus atrophy and inflammation upon exposure to gluten. It has a global prevalence of approximately 1%. Although the gluten-free diet can be an effective treatment, this diet is burdensome with practical difficulties and frequent inadvertent gluten exposure. Moreover, there are a variety of potential complications and comorbidities of coeliac disease that might be related to malabsorption and/or chronic immune activation. Overall, individuals with coeliac disease have increased mortality compared with the general population, underscoring the severity of this common disease. Comorbidities and complications that have been associated with coeliac disease include poor growth, reproductive complications, kidney and liver diseases, respiratory disease (such as pneumonia) and infections (including sepsis). Furthermore, coeliac disease has been linked to other autoimmune disease and psychiatric disease, as well as certain cancers. Data suggest that mucosal healing on a gluten-free diet might protect against some, but not all, of these complications. In this Review, we present absolute and relative risks of coeliac-associated disorders. We discuss underlying mechanisms, the role of the gluten-free diet and mucosal healing, as well as implications for follow-up and non-dietary treatment of coeliac disease.

Sections

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [2]Celiac Disease Center, Department of Medicine, Columbia University Medical Center, New York, NY, USA. [3]Department of Paediatrics, Orebro University Hospital, Orebro, Sweden. [4]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. [5]Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [6]Takeda Pharmaceuticals, Cambridge, MA, USA. [7]Celiac Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.
✉e-mail: jonasludvigsson@yahoo.com

Key points

- Coeliac disease is an autoimmune condition characterized by small intestinal villus atrophy and inflammation of varying severity but with the potential to result in significant complications.
- Complications of coeliac disease include adverse reproductive outcomes, kidney and liver disease, infections, other autoimmune disease, certain cancers and neurological and psychiatric disease, reflecting the multisystemic nature of the disease.
- A combination of chronic immune activation and villus atrophy with resulting malabsorption might explain some of the complications seen in coeliac disease.
- Control of coeliac disease demonstrated by mucosal healing on follow-up biopsy might reduce the risk of some, but not all, complications.

Introduction

Coeliac disease is an autoimmune disease that is characterized by small intestinal villus atrophy and inflammation upon exposure to gluten[1,2] (Fig. 1). Coeliac disease has a wide range of manifestations and can be severe, with potentially substantial complications, disruptive symptoms and adverse effects on overall quality of life. Symptoms include diarrhoea, growth failure, signs of malabsorption, fatigue, psychiatric disease and osteoporosis. The European Society for the Study of Celiac Disease and the American College of Gastroenterology recommend screening for coeliac disease in over 25 conditions[3,4].

Over the years, there has been a growing awareness of comorbidities and complications in coeliac disease, including death[5]. Comorbidities range from autoimmune conditions, in particular type 1 diabetes mellitus (T1DM) and thyroid disease[6,7] but also systemic lupus erythematosus and autoimmune hepatitis[8–10], certain cancers (particularly non-Hodgkin lymphoma and small bowel cancer[11,12]), psychiatric disease[13] and adverse pregnancy outcomes[14].

In the past few years emerging data from epidemiological studies have identified new risks and have also — potentially even more importantly — reported (often modest) absolute risks, which can help clinicians manage coeliac disease and inform patients and the healthcare community of the expected disease course. New knowledge about coeliac disease has implications for healthcare planning, especially as data suggest that coeliac disease is linked to work loss, increased healthcare demand and subsequent healthcare costs[15,16].

In this Review, we provide an update on the complications and comorbidities in coeliac disease. This updated overview is relevant owing to the growing number of trials of pharmaceutical treatments for coeliac disease, the primary aim of which is the prevention or reduction of gluten-induced symptoms, but they also have the potential to decrease the risk of future complications.

Incidence and prevalence

A meta-analysis by Singh and colleagues (n = 96 studies) found that the global prevalence of biopsy-verified coeliac disease in the general population was 0.7%, rising to 1.4% when defining coeliac disease solely based on anti-tissue transglutaminase or anti-endomysial antibody levels[17]. The incidence of coeliac disease has increased[18], with rates of 19 per 100,000 person-years in Sweden in 1990–2015[19] and similar levels in Olmsted County (Minnesota, USA)[20]. On the basis of the data from Sweden, it has been estimated that 1 in 44 women and 1 in 72 men would be diagnosed with coeliac disease throughout their lifetime[19]. Current estimates suggest that approximately 3 million Americans have diagnosed or undiagnosed coeliac disease[4], resulting in a substantial economic burden on individuals and the healthcare system[15]. Traditionally, coeliac disease was a disease affecting younger people, but is now often diagnosed during mid-to-older age[4]. Delays in diagnosis in older people may increase morbidity and mortality[21]. This change in diagnosis and an overall increase in prevalence have important implications for the burden of complications and comorbidities associated with coeliac disease.

Complications and comorbidities

Development and weight

Growth failure is often a sign of chronic disease in children[22]. It is particularly common among children with undiagnosed coeliac disease[23] and indicates the need for coeliac testing. According to a 1988 landmark paper by Maki and colleagues[24], paediatric coeliac disease presented with abdominal symptoms and weight loss until the mid-1970s. But after the mid-1970s, children with coeliac disease more-often presented with short stature and symptoms that were unrelated to malabsorption. In an initial paediatric study from Sweden, 95% of children <2 years of age at the time of coeliac disease diagnosis had poor weight gain[25]. Data from a cohort based in Olmsted County (2000–2010) has shown that the proportion of newly diagnosed individuals with coeliac disease who exhibit malabsorption has decreased[20]. This shift in symptoms might largely be due to the elevated incidence of coeliac disease in relation to the increase in true prevalence, as well as increased rates of diagnosis facilitated by accurate serological testing and a heightened awareness that the disease can present with a range of symptoms and signs[26,27]. Growth failure and poor weight gain can have permanent consequences. In one study, undiagnosed coeliac disease was associated with being underweight in men and women[28]. One study from the United States demonstrated that male adults with coeliac disease were shorter on average than their peers in the general population[29].

Malabsorptive features still occur in new-onset coeliac disease and are often used to classify the clinical picture of the disease (Fig. 2). According to the Oslo classification, coeliac disease presenting with signs and symptoms of malabsorption (diarrhoea, steatorrhea, weight loss or growth failure) is called 'classical coeliac disease'. In contrast, coeliac disease presenting with other symptoms is often called 'non-classical'[2].

Malabsorption in undiagnosed coeliac disease often means that individuals diagnosed with coeliac disease subsequently gain weight by establishing a gluten-free diet (GFD). Such weight gain can be healthy or unhealthy. Some GFD foods over-compensate for the lack of gluten with sugar and fat; and the consequent calorie excess might harm health. Lebwohl and colleagues have demonstrated that long-term avoidance of gluten in individuals without coeliac disease might have adverse cardiovascular effects[30].

Reproduction

Coeliac disease has been linked to reproductive disorders[31,32]. However, several studies have demonstrated normal fertility in women with diagnosed or undiagnosed coeliac disease[33–37]. When Glimberg and colleagues[38] reviewed the literature, they found a prevalence of biopsy-verified coeliac disease of 0.7% and serology-based coeliac

disease of 1.1% in women with infertility, which is similar to that of the general population[17]. The one period when women with coeliac disease might have a lower pregnancy rate is around the time of diagnosis[35], potentially because they might abstain from pregnancy due to ongoing investigations for suspected coeliac disease or postpone pregnancy because of nutritional concerns[36]. Interestingly, some earlier data have suggested that men with coeliac disease might have decreased semen quality[39], but little research has been performed in this field. Although a study has demonstrated that sperm chromatin maturation and DNA fragmentation in men is affected by coeliac disease[40], this does not seem to translate into lower fertility[41].

Even with normal fertility, coeliac disease could still affect the reproductive lives of women. For example, Grode and colleagues have suggested that undiagnosed coeliac disease is linked to an increased prevalence of spontaneous abortion (1 extra spontaneous abortion per 100 pregnancies in women with coeliac disease)[35]. In a later study of 791 pregnancies in women with coeliac disease in Norway, the odds ratio (OR) for miscarriage was increased by 16% but failed to attain statistical significance[42].

Coeliac disease might also affect pregnancy and pregnancy outcomes. In 2005, Ludvigsson and colleagues reported that placental weight in women with undiagnosed coeliac disease was lower than in women from the general population or women with diagnosed coeliac disease[43]. This finding could explain the lower birthweight in offspring of mothers who were later diagnosed with coeliac disease (but who likely had undiagnosed coeliac disease during pregnancy)[43]. Undiagnosed coeliac disease might also be linked to preterm birth[43]. In addition, two large studies from the United States have reported an increased risk of poor intrauterine growth in the offspring of mothers with coeliac disease[44,45]. These data, which report adverse outcomes in offspring of women with diagnosed coeliac disease, contrast with earlier population-based studies. For example, in Sweden, adverse pregnancy outcome was restricted to births that occurred before coeliac disease diagnosis in the mother[43]. Somewhat surprisingly, however, mucosal healing in diagnosed women – a proxy for dietary adherence in coeliac disease – does not seem to affect pregnancy outcomes in coeliac disease[46].

Eyes

Individuals with coeliac disease are at increased risk of cataracts and uveitis[47,48]. A positive association has also been seen for Sjögren syndrome, which results in dry eyes and mouth. In one study the prevalence of coeliac disease in individuals with primary Sjögren syndrome was 6.78% compared with 0.64% in controls between 15–90 years old from 10 Italian primary healthcare centres[49], whereas another study found that only 5 out of 437 (1.1%) of individuals with primary Sjögren

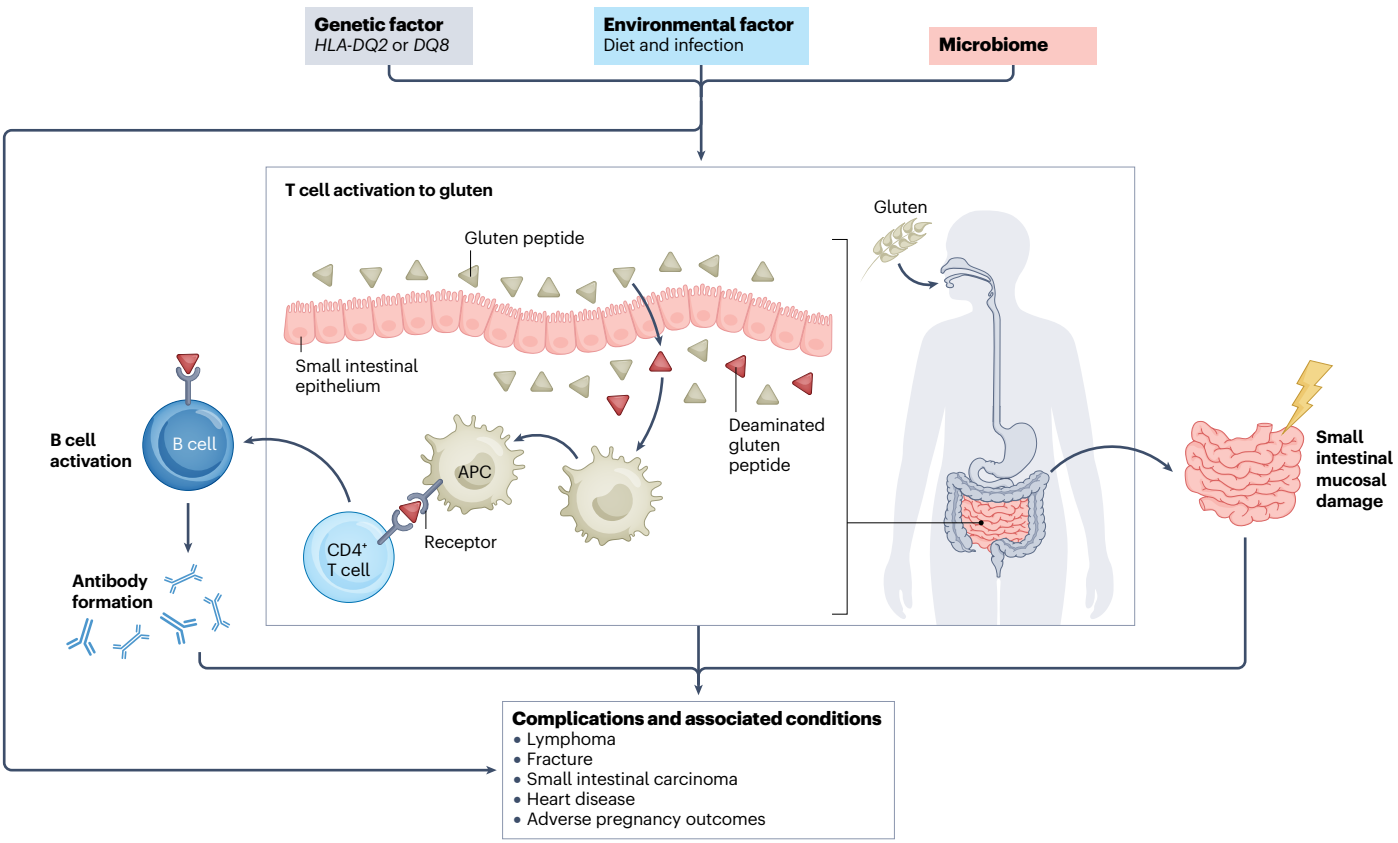

Fig. 1 | Proposed pathophysiological mechanisms of coeliac disease and its associated complications and comorbidities. Incomplete digestion of gluten peptides in genetically predisposed individuals triggers adaptive immune responses in the lamina propria. Additional environmental factors, such as diet and infections, might also have a role in the pathogenesis of coeliac disease. The upregulated inflammatory status causes damage to the small intestinal mucosa and is involved in the development of coeliac disease complications and comorbidities. APC, antigen-presenting cell.

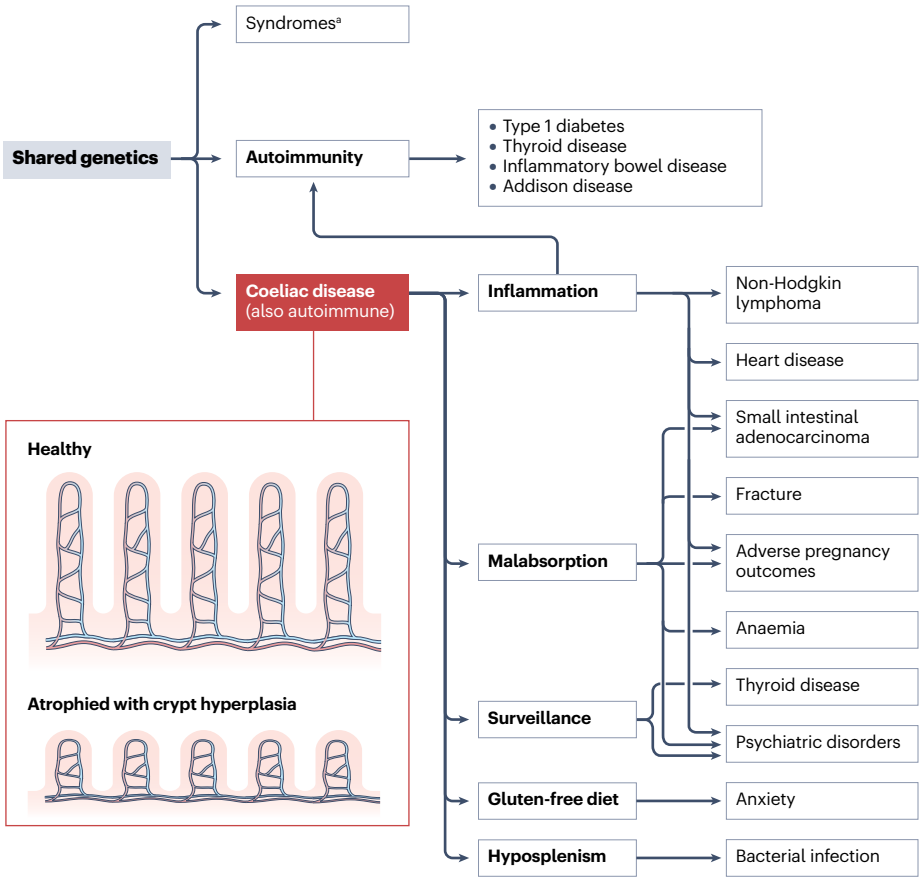

Fig. 2 | Summary of the main complications and comorbidities associated with coeliac disease. The main complications and comorbidities in coeliac disease, with bold text representing the common risk factor (such as genetics) or mediators (such as inflammation and malabsorption). [a]Down syndrome and Turner syndrome.

syndrome had coeliac disease[50]. Finally, a large UK population-based study reported increased risks for Sjögren syndrome (incidence rate ratio (IRR) 3.9) and Graves disease (IRR 2.5)[51] in 31,447 individuals with coeliac disease.

Mouth

Oral manifestations of coeliac disease include recurrent aphthous ulcers and dental enamel defects[52]. The latter has been shown to have an immune basis due to the presence of autoantibodies, mostly IgA, against proteins from ameloblasts[53], which are cells that produce enamel during tooth development.

Haematological associations

Anaemia and micronutrient deficiencies are common in newly diagnosed individuals with coeliac disease, with anaemia detected in 20–30% of individuals at the time of presentation[54–56]. Among individuals with coeliac disease and anaemia, iron deficiency[56], folate and B_{12} deficiencies in particular are also observed, as well as anaemia of chronic diseases often due to long-term inflammation. These nutritional deficiencies are present in >50% of individuals with coeliac disease and might be related to malabsorption, nutritional limitations of the GFD, or both[57]. In contrast with the general population, iron deficiency in coeliac disease might be more frequent in men than women[55]. Elevated ferritin values should alert physicians to hereditary haemochromatosis, which is associated with coeliac disease[58]. Similarly, thrombocytosis could be a sign of undiagnosed coeliac disease[59].

Kidney and hepatobiliary disease

Although data on the risk of gallstones in coeliac disease are conflicting[60–62], data suggest a moderately elevated risk of kidney stones before and after coeliac disease diagnosis[63]. The kidney stones are probably due to hyperoxaluria, and a GFD probably reduces oxaluria and kidney stone disease[64]. Moreover, individuals with coeliac disease are at increased risk of glomerulonephritis and IgA nephropathy[65,66], although the excess risks of these diseases could depend on the coeliac disease phenotype as no risk increase has been demonstrated in dermatitis herpetiformis[65] (a condition often seen as a form of coeliac disease but characterized by itchy skin lesions). It is therefore not surprising that individuals with coeliac disease are also at an increased risk of end-stage renal disease[67].

Liver disease is frequently observed in individuals with coeliac disease. Individuals with coeliac disease had higher transaminase levels in the UK Biobank than controls[61]. Typically, these enzymes normalize with a GFD[68,69]. In addition, the incidences of nonalcoholic (metabolic dysfunction-associated) steatohepatitis and hepatocellular carcinoma are increased in coeliac disease[61,70]. An analysis of the UK Biobank cohort revealed positive associations between coeliac disease and nonspecific chronic hepatitis, autoimmune hepatitis and cirrhosis[61], findings later confirmed in a meta-analysis[9]. Data from Denmark and Sweden have shown an excess risk of primary biliary cholangitis[71], with data from Denmark also linking coeliac disease to alcoholic cirrhosis (adjusted IRR 5.12)[72]. Notably, in a study from Finland that reported four patients with severe liver disease and coeliac disease, liver function improved with a

GFD[73]. These studies suggest that coeliac disease should be considered when caring for patients with chronic liver disease.

Respiratory disease

Coeliac disease has been linked to asthma[60], bacterial pneumonia[74,75] (and pneumococcal infections in general[76]), chronic obstructive pulmonary disease[77] and tuberculosis[78]. These comorbidities are often higher in frequency both before and after coeliac disease diagnosis. One study suggested that community-acquired pneumonia is particularly common in individuals with coeliac disease who are aged >65 years without earlier pneumococcal vaccination[75]. On the other hand, vaccinated individuals with coeliac disease show no such increase in risk[75]. In addition, several studies have suggested a link between coeliac disease and death from respiratory disease[5,79].

Musculoskeletal and joints

Rheumatological complaints are common in children and adults with coeliac disease[80], and arthritis — both peripheral and axial rheumatic disease — seems to be more common in individuals with coeliac disease[81]. Children have an increased risk of juvenile idiopathic arthritis, whereas adults have an increased rate of rheumatoid arthritis[82]. Individuals with coeliac disease are also at higher risk of Ehlers-Danlos syndrome and joint hypermobility than the general population[83]. Finally, enthesopathy is more frequent in individuals with untreated coeliac disease than those on a GFD[84].

Metabolic bone disease, which is common in coeliac disease — the prevalence of osteopenia or osteoporosis ranges from 38–72% of newly diagnosed individuals — is associated with increased fracture risk in individuals with coeliac disease[85,86]. Although there are data suggesting that bone mineral density in coeliac disease improves with a GFD[87], over the long term treated coeliac disease has been linked to fractures[88] and persistent villus atrophy in follow-up biopsy samples has conferred an increased risk of hip fracture but not overall fracture risk[89]. It is possible that inflammation and immune-mediated mechanisms might have a role in the development of bone problems in coeliac disease[90]. Notably, the prevalence of coeliac disease in those with osteoporosis is approximately the same as in the general population[91]. Hence, we do not recommend screening for coeliac disease in individuals with osteoporosis and no other signs of coeliac disease.

Autoimmunity

The association between coeliac disease and other autoimmune conditions is well established (see sections on thyroid disease and T1DM). This association probably stems from genetic and environmental factors rather than a causative effect of one autoimmune disease on another (Fig. 2). First-degree relatives of individuals with coeliac disease seem to be at a small increased risk of autoimmunity[92] (suggesting that ongoing inflammation is unlikely to be the only cause of autoimmunity). Spouses of individuals with coeliac disease also have a small increased risk of autoimmunity, indicating that shared environmental factors and healthcare-seeking pattern could play a role.

Approximately 25% of individuals with coeliac disease have at least one other autoimmune disorder[93–97], most commonly T1DM or autoimmune thyroid disease. Another autoimmune disease that is associated with coeliac disease is inflammatory bowel disease (IBD)[98,99]. In a study including >48,000 individuals with coeliac disease and approximately 83,000 individuals with IBD[98], individuals with coeliac disease were at a four-fold increased risk of later IBD even beyond the first year after diagnosis. In contrast, individuals with IBD were at a five-fold increased risk of later coeliac disease. Up to 1 in 40 individuals with coeliac disease had a later diagnosis of IBD, with the highest hazard ratio (HR) for Crohn's disease (HR 4.36; 95% CI 3.72–5.11). individuals with coeliac disease are also at a highly increased risk (almost 12-fold) of microscopic colitis[100], potentially due to shared genetics and lymphocytic infiltration in the colon caused by active coeliac disease, although increased medical surveillance of patients with coeliac disease may also have contributed.

Although there is little evidence that improved control of coeliac disease can reduce the risk of developing additional autoimmune disease[101,102], assessment of autoimmune conditions should be considered in the follow-up of patients with coeliac disease to enable prompt management of these conditions.

Diabetes, endocrine and hormonal disorders

Research has suggested that there is an association between T1DM and coeliac disease[103–105]. Although it has been hypothesized that untreated coeliac disease heightens the risk of T1DM, there is no firm evidence that this is the case and it is more probable that these two conditions co-occur due to shared genetic and environmental risk factors[106]. However, clinicians need to be aware of this association, as prompt diagnosis and management are critical for improving disease outcomes.

A systematic review and meta-analysis of 27 studies totalling 26,605 individuals with T1DM found a pooled prevalence of biopsy-confirmed coeliac disease of 6%, which is far higher than the approximately 1% prevalence in the general population[6]. The risk of developing T1DM remains high after diagnosis of coeliac disease, with one population-based study of 9,243 children with inpatient diagnosis of coeliac disease reporting an HR of 2.4 for T1DM diagnosed before the age of 20 years[105].

Specifically, longstanding coeliac disease is associated with higher risks of T1DM complications, including retinopathy, nephropathy and death[107,108], which is likely to be related to worse glycaemic control[109]. Conversely, the dual burden of both conditions leads to a reduced quality of life[110,111], reduced quality of a GFD[109,112] and in some cases might cause an elevated risk of gluten exposure, leading to worsened control of coeliac disease[107,113–115]. Coeliac disease can also be a component of autoimmune polyglandular syndrome type 2, a condition that is principally characterized by T1DM, Addison disease and autoimmune thyroid disease[116].

In addition to T1DM, coeliac disease can also co-occur with type 2 diabetes mellitus (T2DM). Although rates of T2DM in individuals with coeliac disease are similar to or lower than in the general population[107,117,118], overlap might have increased in recent years with an increased overall prevalence of T2D. There are little published data on the clinical effect of co-existing coeliac disease and T2DM. However, because a GFD can increase cholesterol and body mass index (BMI)[107,119], greater attention to weight control and GFD quality in individuals with coeliac disease and T2DM should be considered.

Thyroid disease is the most common concurrent autoimmune comorbidity in individuals with coeliac disease. An analysis of the National Health and Nutrition Examination Survey (2009–2014) from the United States found that 14 of the 77 individuals with coeliac disease had self-reported thyroid disease (population-weighted prevalence: 20.5%)[120]. The analysis included individuals with prior diagnosis of coeliac disease by a healthcare professional and those with undiagnosed coeliac disease based on elevated serum anti-transglutaminase and anti-endomysial antibody levels. A study designed to examine individuals with undiagnosed coeliac disease in the United States noted that this population had an increased prevalence of hypothyroidism (OR 1.97)[21].

Primary hyperparathyroidism has been investigated in a population-based study in Sweden. This study found that individuals with coeliac disease had an increased risk of primary hyperparathyroidism (HR 1.91), with an absolute excess risk of 20 per 100,000 person-years compared with coeliac disease-free general population reference individuals[121]. The study has also shown that the risk increase for this condition was confined to the first 5 years after coeliac disease diagnosis.

Cancer

Coeliac disease is statistically significantly associated with increased risks of intestinal and extraintestinal cancers, but relative and absolute excess risks are very low[122,123] (Box 1). A population-based study in Sweden reported that, overall, coeliac disease was linked to cancer development only in the first year after diagnosis[123].

These differential risks appear to be related to coeliac disease per se rather than genetic disposition, as first-degree relatives of individuals with coeliac disease have a cancer risk similar to that of the general population[124]. As with most autoimmune disorders, the cancer risk in coeliac disease is highest in disease-related organs (that is, the immune system and small intestine) compared with more distant organ systems[125].

Although the relative risk of some cancers is statistically significantly elevated in individuals with coeliac disease, it is important when counselling patients to recall that the absolute risk is low and that most individuals with coeliac disease who develop cancer have the most common cancer types, as in the general population, which are not specifically related to coeliac disease. It has been estimated that coeliac disease per se is linked to 1 extra case of cancer in every 125 individuals with coeliac disease continuously followed for 10 years[123].

For this reason, with the exception of individuals with histologically confirmed refractory coeliac disease, there are currently no recommendations for cancer screening in individuals with coeliac disease beyond those of the general population.

Nutrition

Coeliac disease can interact with nutritional status owing to the reduced absorption capacity of the small intestine due to mucosal injury, or through the differential dietary quality of a GFD compared with a traditional diet[126,127]. For these reasons, nutritional status should be assessed at the time of diagnosis and over time as nutritional consequences can evolve in coeliac disease. Active coeliac disease can lead to deficiencies in iron, folate, vitamin D and zinc[128,129], as well as other micronutrients including vitamins B_{12} and B_6, vitamins A and K, copper and magnesium[57]. Estimates of the prevalence of these deficiencies in both children and adults with coeliac disease vary greatly, ranging from <10% to >80%[130,131], depending in large part on regional differences in diet, supplementation and fortification. For these reasons, best practice for nutritional testing in coeliac disease should be based on local epidemiology whenever possible. In severe cases, coeliac disease can lead to overall malabsorption of proteins and energy, steatorrhea and related deficiencies in fat-soluble vitamins[132]. Although many deficiencies are expected to improve with control of coeliac disease, supplementation might be needed, particularly early after diagnosis or in individuals with ongoing active coeliac disease.

In addition to the consequences of small intestinal mucosal damage, the GFD might itself increase the risk of nutritional concerns[126,128,133]. In particular, the GFD can be low in fibre and B vitamins but high in fats and refined sugars, leading to constipation, vitamin deficiencies, weight gain and elevated cholesterol levels[126,128,133]. There is growing awareness that coeliac disease might lead to disordered eating, a condition that has nutritional consequences[134]. For these reasons, ongoing consultation with a dietitian who is experienced in coeliac disease is necessary for patients and follow-up laboratory tests should consider risk factors, including deficiencies at the time of diagnosis and dietary habits[4,135].

Cardiovascular disease

Multiple studies support a modest increased risk of cardiovascular disease (CVD) in individuals with coeliac disease. A population-based study of Swedish individuals found an increased risk of myocardial infarction or angina (HR 1.19), with an absolute excess risk of 60 per 100,000 person-years, equal to 1 extra case of myocardial infarction in about 170 individuals with coeliac disease followed-up for 10 years[136]. An analysis of the same population reported an increased risk of stroke (HR 1.10), with an absolute excess risk of 24 per 100,000 person-years[137]. An analysis of an updated and expanded Swedish histopathology cohort (ESPRESSO)[138] established that the cardiovascular mortality risk in coeliac disease is increased (HR 1.08), with an absolute excess risk of 10 per 100,000 person-years, or one extra death from CVD in 1,000 individuals with coeliac disease followed-up for 10 years[5]. Data from Finland have indicated that the excess CVD risk is limited to individuals with coeliac disease and not seen in individuals with dermatitis herpetiformis[139].

The mechanism for the increased risk of CVD might differ from that for the general population. Among Swedish individuals with ischaemic heart disease, those with coeliac disease had lower serum cholesterol, lower BMI and were less likely to smoke[140]. Similarly, an analysis of the UK Biobank detected an increased risk of CVD among individuals with coeliac disease (HR 1.27) despite lower rates of smoking, lower blood pressure and lower BMI in this population (when adjusting for traditional CVD risk factors, the risk estimate increased to 1.44)[141]. Hence, the explanation for the observed excess CVD risk should be sought elsewhere, potentially in the chronic inflammation that is associated with coeliac disease or nutritional deficiencies[142] (Fig. 2).

Genetic conditions

Down syndrome and Turner syndrome carry an increased risk of coeliac disease. A registry-based cross-sectional study on individuals with

Box 1 | Associations between coeliac disease and different types of cancer

Cancer types that have been investigated in association with coeliac disease are listed and arranged by the direction and statistical significance of the association, as well as the consistency of existing evidence.

- Strong and consistently positive: non-Hodgkin lymphoma[12], enteropathy-associated T cell lymphoma[199,200] and small intestinal adenocarcinoma[11].
- Weak or inconsistently positive: oesophageal cancer[201], thyroid cancer[7], pancreatic cancer[123] and liver cancer[123].
- Neutral: colorectal cancer[123], prostate cancer[202], melanoma[203], gastric cancer[123] and lung cancer[123].
- Weak or inconsistently negative: endometrial or ovarian cancer[204].
- Strong and consistently negative: breast cancer[123].

Down syndrome in New York state found that 5% of the study population were diagnosed with coeliac disease, according to parental reports[143]. Similarly, in Olmsted County, Minnesota, 7% (3 out of 45) of individuals with Down syndrome had been diagnosed with coeliac disease[144]. A record-linked dataset of hospital admissions in England reported that individuals with Turner syndrome had a 14-fold increased risk of coeliac disease[145]. However, this risk increase was substantially lower (approximately 3-fold) in a Swedish nationwide case-control study[146].

Psychiatric disease

Many studies of varying methodologies and settings have detected associations between coeliac disease and several psychiatric morbidities. For example, a GFD prescription might worsen the latent tendency to disordered eating. A nationwide population-based study in Sweden observed an increased risk of anorexia nervosa after the diagnosis of coeliac disease (HR 1.46; absolute risk difference: 9 per 100,000 person-years)[147].

An analysis within the Swedish nationwide histopathology cohort ESPRESSO[138] noted that the risk of psychiatric disorders was increased in individuals diagnosed with coeliac disease in childhood (HR 1.19, equal to one extra psychiatric event in 52 individuals with coeliac disease followed for 10 years)[13]. An increase in specific disorders included mood disorders (HR 1.20), anxiety disorders (HR 1.12), eating disorders (HR 1.34), attention deficit hyperactivity disorder (HR 1.29) and autism spectrum disorder (HR 1.47). The overall risk of psychiatric disorders increased immediately after coeliac disease diagnosis but was also observed over the long term. In children diagnosed with coeliac disease who reached the age of 18 years without a diagnosis of psychiatric disease, the risk of a psychiatric disease diagnosis in adulthood (≥18 years) increased (HR 1.11; absolute excess risk: 1.8 per 1000 person-years)[13].

In contrast, the risk of schizophrenia does not seem to increase after a diagnosis of coeliac disease; no association was found in the previously discussed Swedish study or in a population-based study in Denmark[13,148].

Neurological disorders

Peripheral neuropathy and ataxia are two common neurological manifestations in coeliac disease, which are presumably mediated by autoimmunity against brain-expressed transglutaminase 6 (refs. 149,150). Gluten neuropathy and gluten ataxia represent 19–30% and 19–40%, respectively, of neurological conditions in individuals with coeliac disease[151]. A Swedish nationwide histopathology cohort reported a 2.5-fold increased risk of developing peripheral neuropathy in individuals with coeliac disease compared with the general population[152], while relative risk estimates for ataxia remain scarce. Both conditions primarily affect older populations, and some single-centre experiences suggest an ameliorating effect of a GFD[149,151].

In addition to these neurological manifestations, there is evidence for profound organic changes in the brain of individuals with coeliac disease, indicated by white matter abnormalities and cerebral hypoperfusion[149,153,154]. In Sweden, individuals with biopsy-confirmed coeliac disease had a higher risk of headache-related healthcare visits both before and after diagnosis (OR 1.65 and HR 1.66, respectively). This finding was later corroborated by a Danish nationwide cohort, which reported a 49% increased risk of incident migraine in individuals with coeliac disease[148,155]. Positive associations have also been observed between coeliac disease and other neurological disorders, such as epilepsy[148,156,157] and vascular dementia[158]. However, findings on the association between coeliac disease and stroke are inconsistent[139,141], and despite the autoimmune nature of amyotrophic lateral sclerosis and myasthenia gravis, there is no evidence linking them to coeliac disease[159,160].

Skin disorders

Dermatitis herpetiformis is a cutaneous disorder with a pathophysiology that is partially shared with coeliac disease[161]. Common skin diseases are associated with coeliac disease. A population-based study in Sweden found that individuals with coeliac disease had an increased risk of skin disorders (HR 1.55; absolute risk difference of 7.8 per 1,000 person-years)[162]. In addition to dermatitis herpetiformis, this study also found an increased risk for other skin diseases, including eczema, psoriasis, urticaria, vitiligo, acne and alopecia areata. In an analysis of a large health management organisation in Israel, the association between coeliac disease and atopic dermatitis was stronger among individuals with moderate-to-severe skin disease, with a prevalence of diagnosed coeliac disease of 0.8% in that group compared with 0.3% in individuals without atopic dermatitis[163].

Refractory coeliac disease

Refractory coeliac disease refers to the presence of persistent symptoms related to malabsorption and villus atrophy despite adherence to the GFD for >12 months. The condition is rare, affecting <2% of individuals with coeliac disease[164]. Most individuals with refractory coeliac disease have normal or near-normal coeliac disease-related serologies, as these values decline after adoption of the GFD. The condition is classified according to the molecular characteristics of intraepithelial T cell populations, with type 1 consisting of a polyclonal population and type 2 characterized by a monoclonal population[165]. Mortality risk in type II refractory coeliac disease is high, and current therapies are limited in efficacy[166].

Mucosal healing

For most individuals with coeliac disease, adopting a GFD leads to clinical improvement and histological resolution of villus atrophy. Because clinical improvement and serological normalisation do not reliably predict mucosal healing[167,168], a follow-up biopsy to assess for this histological outcome has been advocated, given its potential clinical utility[169]. Guidelines published by the American College of Gastroenterology in 2023 suggest setting the goal of mucosal healing as an end point of therapy, but also that the patient and provider engage in shared decision making to assess mucosal healing in the absence of symptoms[4]. However, routine follow-up biopsy to confirm healing is not universally advocated. A guideline on monitoring of coeliac disease, issued by an international panel of coeliac disease experts, recommended against the use of a routine re-biopsy strategy in individuals with coeliac disease on a GFD, suggesting instead that the decision be based on clinical findings and risk factors[170].

Comparisons of patients with mucosal healing to those with persistent villus atrophy have been assessed on various outcomes (Fig. 3). Most studies were conducted in the population-based cohorts established in Sweden, using either the ESPRESSO cohort[138] or its antecedent[171]. These studies evaluated all patients who had a follow-up biopsy 6 months to 5 years after the initial biopsy, which comprised approximately 25% of all individuals with an initial diagnosis of villus atrophy. Persistent villus atrophy was present in 43% of individuals on their follow-up biopsy[171]. Individuals with persistent villus atrophy tended to be older, had a shorter duration of coeliac disease and had a lower education level compared with individuals with mucosal healing[171].

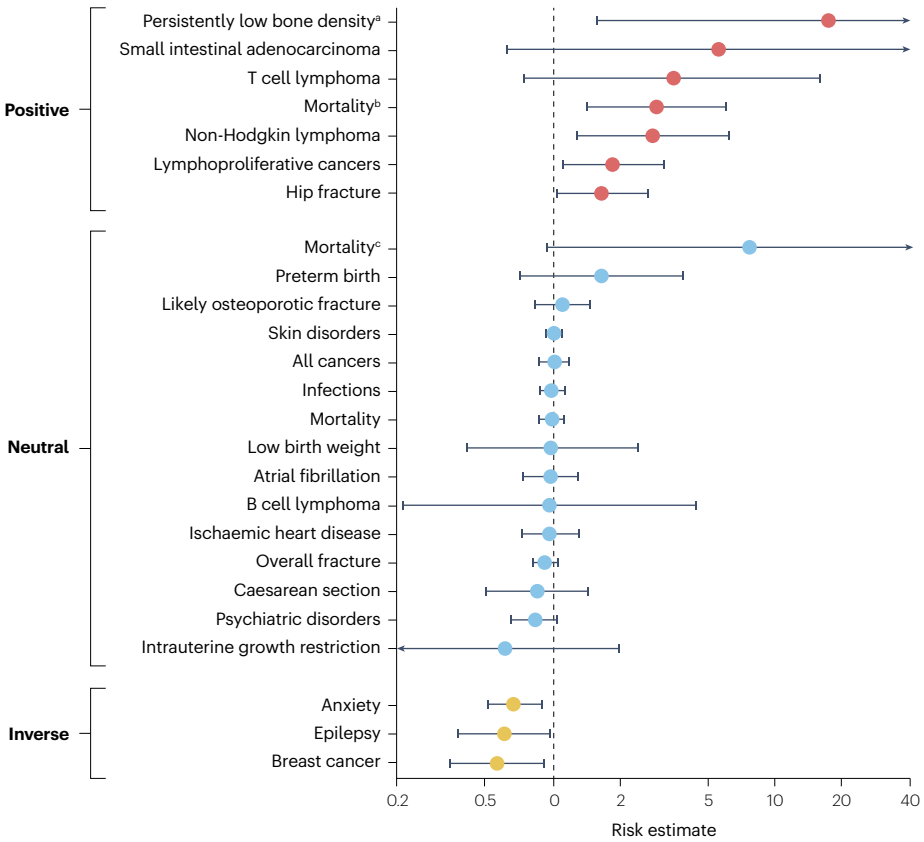

Fig. 3 | Associations between persistent villus atrophy and health outcomes. Health outcomes that have been investigated in association with persistent villus atrophy (compared with mucosal healing) are listed and arranged by the direction, magnitude and statistical significance of the associations (from top to bottom, those with positive, neutral and inverse associations are denoted by red, blue and yellow circles, respectively). Risk estimates refer to hazard ratios or relative risk in all studies except for pregnancy-related outcomes (preterm birth, low birthweight, caesarean section and intrauterine growth restriction), where odds ratios are given. Data from: persistently low bone density[193], small intestinal adenocarcinoma[11], T cell lymphoma[172], mortality[5,167,194], non-Hodgkin lymphoma[172], lymphoproliferative cancers[123], hip fracture[89], preterm birth[46], likely osteoporotic fracture[89], skin disorders[162], all cancers[123], infections[195], atrial fibrillation[196], low birthweight[46], ischaemic heart disease[196], B cell lymphoma[172], overall fracture[89], caesarean section[46], psychiatric disoders[197], intrauterine growth restriction[46], anxiety[173], epilepsy[198] and breast cancer[123]. [a]Data from Italy. [b]Data from Italy, the UK and the USA. [c]Data from the USA. Data for all other studies from Sweden.

Multivariate analyses that assessed the outcomes of individuals with persistent villus atrophy compared with those with mucosal healing revealed increased risks of lymphoproliferative malignancy (HR 1.87)[123], and specifically non-Hodgkin lymphoma (HR 2.82) and possibly T cell lymphoma (HR 3.51)[172], as well as small intestinal adenocarcinoma (HR 5.55). Persistent villus atrophy was also associated with hip fracture (HR 1.67)[89]. Although overall mortality in coeliac disease is increased compared with matched controls, the relationship between persistent villus atrophy and mortality remains uncertain, with some data suggesting no increased risk[5] and other work demonstrating a substantial increase in mortality with persistent villus atrophy[167]. However, persistent villus atrophy was associated with a lower risk of epilepsy (HR 0.61) and breast cancer (HR 0.56)[123]. The latter observation might be due to relative malabsorption and decreased breast tissue, although this is speculative. Beyond the scope of malignancies, mucosal healing has also been associated with an increased risk of anxiety (HR 1.49)[173] (Fig. 2). This association might be related to the hypervigilance that can both promote and be a by-product of stringent adherence to the GFD[174]. More research on the pros and cons of a strict GFD in coeliac disease is needed.

Implications for new treatments

Currently, the only treatment for coeliac disease is a lifelong GFD, but this is often ineffective at achieving symptom control and mucosal healing. Persistent and recurrent symptoms are commonly reported, and in one analysis based in a coeliac disease referral centre, over half of the individuals who followed a self-reported GFD had ongoing symptoms, which are often the same as those that prompted their diagnosis[175]. The causes of these symptoms are heterogeneous and include concurrent common functional disorders (such as irritable bowel syndrome), but ongoing gluten exposure is often identified as a culprit[176]. Studies on the detection of traces of gluten in food and biospecimens have established that gluten exposure is common, even among those reporting strict adherence to the GFD[177,178]. As such, it is now perceived that a true GFD is virtually impossible and that a more realistic approach is to adopt strategies to minimize gluten exposure. Studies have shown that gluten exposure is often identified even in individuals who follow a GFD or in gluten-free labelled food itself[178,179].

Given the substantial limitations and practical difficulties of the GFD, there have been major efforts to develop non-dietary therapies adjunctive to the GFD. Although a full review of the research and development span and status of these treatments is beyond the scope of this article (reviewed elsewhere[180]), broad categories of therapeutics in development include: drugs that act on gluten via peptidase/protease activity, rendering the peptide fragments non-immunogenic (such as latiglutenase[181] and TAK-062 (ref. 182)); drugs that promote tolerance by a parenteral presentation of gluten to suppress the inflammatory cascade (such as Nexvax2 (ref. 183), TAK-101 (ref. 184) and KAN-101 (ref. 185)); blockers of cytokines thought to be central in the immune response to gluten, such as IL-15 (including AMG-714/PRV-015 (ref. 186) and CALY-002 (ref. 187)); and blockers of the downstream processing of gluten fragments by tissue transglutaminase and its presentation by antigen-presenting cells (such as ZED-1227/TAK-227 (ref. 188) and DONQ52 (ref. 189)).

Typically, trials testing these therapeutics measure symptoms and histological outcomes in line with regulatory guidance[190]. These criteria imply that if therapeutics are approved, it will remain unclear whether they will alter the patterns of complications and comorbidities outlined in this Review. Although mucosal healing is correlated with a reduced incidence of lymphoproliferative malignancy[172] and osteoporotic fracture[89], these outcomes would not be measurable within the relatively short time horizon of a clinical trial. These long-term outcomes, along with the increasing prevalence of coeliac disease and control over the comorbidities discussed in this Review, will be of keen interest when examining the overall health effects of adjunctive therapies and warrant adequately powered post-marketing studies.

Perspectives and future directions

Coeliac disease is associated with a wide range of disorders. Although the relative and absolute risks are often low to moderate, the high number of associated disorders suggests that the proportion of individuals with coeliac disease with comorbidities and complications is large. For example, we expect only one additional case of myocardial infarction for every 170 individuals with coeliac disease and one additional case of cancer for every 125 individuals with coeliac disease within 10 years of follow-up[123,136]. In addition, there is possibly one excess spontaneous abortion per 100 pregnancies in women with coeliac disease[35]. These mildly increased risks are seen in individuals across a wide range of demographics[35,123,136]. However, taken together, the complications and comorbidities collectively constitute a substantial disease burden in individuals with coeliac disease.

In a working-age population the overall burden of coeliac disease translates into an almost 50% increase in work loss, equivalent to an annual work loss of 15 extra days[16]. This gap does not seem to decrease with time since diagnosis (which is presumably equal to time on GFD)[16]. Moreover, the most lost workdays were seen in individuals with the lowest level of education, suggesting that management of coeliac disease might be negatively affected by poor socioeconomic status[16].

The complications and comorbidities of coeliac disease have implications for healthcare. In 2020, Mårild and colleagues demonstrated that individuals with coeliac disease have higher overall healthcare costs than the general population. Cost increases were not primarily attributed to GFD prescriptions in follow-up visits but to comorbidities, complications and associated medication use[15]. To minimize the effect of coeliac disease, patients must be appropriately followed-up and informed about measures to treat coeliac disease and counter the risk of complications and comorbidities. In addition, individuals with coeliac disease should be encouraged to follow a healthy lifestyle, such as maintaining a healthy weight through increased fibre intake and regular physical activities. In addition, in our opinion, individuals with coeliac disease should avoid common adverse risk factors such as tobacco and alcohol. This advice would reduce the risk of CVD and cancer, the predominant causes of death in individuals with coeliac disease[5]. Other preventive measures include vaccinations; vaccinations for infection (for example, pneumococcal and influenza) should be encouraged because these infections have been linked to coeliac disease[75,76,191].

We advocate a GFD for symptom relief and mucosal healing. Mucosal healing has been linked to a lower risk of lymphoproliferative cancer, small intestinal adenocarcinoma and hip fracture[11,89,172]. However, mucosal healing might not protect against all complications and comorbidities, as their underlying mechanisms are varied and might be intertwined with genetic features. It should also be noted that mucosal healing might have side effects such as anxiety[173]. Weight gain following a GFD might also have negative effects (possibly on breast cancer risk)[123], and earlier research by Lebwohl and colleagues showed that a GFD is not beneficial from a cardiovascular perspective in individuals without coeliac disease[30]. The development and implementation of adjunctive therapies hold promise. In clinical trials such drugs are evaluated against coeliac disease-specific measures such as villus-height ratio, antibody levels and symptoms. However, after their market approval, in the longer term such drugs should also be evaluated based on their ability to reduce complications and comorbidities.

Many comorbidities share immunological and genetic features with coeliac disease, which can be linked to the inflammation or malnutrition that characterize coeliac disease. Thus, healthcare is important in preventing comorbidities and complications. One way to achieve this goal is to detect disease early, which prompts screening in high risk groups such as individuals with T1DM and anaemia[6,192]

Conclusions

Coeliac disease is a common and serious autoimmune disease with a potential for substantial complications, burdensome signs and symptoms, and a diminished quality of life. In addition, it is associated with many intestinal and extraintestinal disorders. The absolute risk of each individual disorder is often low but, when taken together, has a substantial burden. In this Review, we have summarized the data on complications and comorbidities of coeliac disease in different organ systems. High awareness of coeliac disease and proper follow-up management are essential to reduce comorbidities and complications.

Published online: 28 January 2025

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Acknowledgements

J.F.L. acknowledges the Karolinska Institutet. J.F.L and J.Y. were supported by an Investigator Initiated Research grant from Takeda Development Center Americas, a member of the Takeda group of companies (IISR-2023-200390).

Author contributions

J.F.L., J.Y., B.L., P.H.R.G. and D.A.L. researched data for the article, made a substantial contribution to discussion of content, wrote the article and reviewed/edited the manuscript before submission. S.Y. made a substantial contribution to discussion of content, wrote the article and reviewed/edited the manuscript before submission.

Competing interests

J.F.L. has coordinated an unrelated study on behalf of the Swedish Inflammatory Bowel Disease quality register (SWIBREG). That study received funding from the Janssen Corporation. J.F.L. has also received financial support from Merck Sharp & Dohme to develop a paper reviewing national healthcare registers in China. J.F.L. also has a research collaboration on coeliac disease with Takeda. D.A.L. receives a salary as an employee of Takeda Pharmaceuticals.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41575-024-01032-w.

Peer review information *Nature Reviews Gastroenterology & Hepatology* thanks Knut Lundin and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Review criteria A search for relevant original articles published since 1 January 2010 was conducted in Medline, Embase and Web of Science databases on 4 July 2023. The search covered terms such as "celiac", "coeliac", "comorbid*", "complicat*", "epidemiolog*", "cohort", "case-control", "hazard model*", either alone or in combinations (see **Supplementary Information** for a detailed description). We identified 273 potentially relevant papers from 2,509 de-duplicated pieces of work. All articles identified were in English and available in full text. Observational studies using a population-based sample and a biopsy-confirmed coeliac disease diagnosis were preferable but not exclusive: non-population-based studies or studies that did not require biopsy for coeliac disease diagnosis were chosen only when no other studies on the topic were identified. In addition to references identified through this search, other relevant studies (published before and after 2010) were cited. The Endnote files with the search results will be shared upon request.