UK National Screening Committee

Screening for coeliac disease

An evidence map to outline the volume and type of evidence related to screening for coeliac disease for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care

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The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of population and targeted screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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Summary

This document discusses the findings of an evidence map completed by the Bristol Evidence Synthesis for Screening (BESS) Group, hosted at the University of Bristol, on screening for coeliac disease.

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, the authors' recommendation is that the current evidence supports the commissioning of further synthesis work on screening for coeliac disease in adults.

Introduction and approach

The UK NSC makes recommendations based on careful review of evidence against specific criteria, with regular updates of the evidence that underpins the recommendations. The UK NSC external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for coeliac disease in adults is a topic currently due for an updated external review.

Importance of evaluating potential screening programmes

"All screening programmes do harm. Some do good as well and, of these, some do more good than harm at reasonable cost."[1] Screening programmes aim to identify people at risk at a stage that optimises the chances of effective treatment and improved patient outcomes. The UK NSC, a committee of independent experts, plays a critical role in determining whether the benefits of a potential screening programme outweigh the harms and justify the associated costs. UK NSC recommendations are based on careful review of evidence against specific criteria.

Several factors affect whether a screening programme is clinically and/or cost effective. These include people's access to and uptake of screening, test accuracy, ease of use, cost and administration, whether the intervention leads to better outcomes compared with treating once symptoms develop, and any other unintended consequences.[1] It is essential to consider the harms that may result from false positives, false reassurance, overtreatment, and complications from tests or treatments. Critically, it cannot be assumed that screen-detection always leads to improved patient outcomes. Overdiagnosis, where screening detects an abnormality that would not have caused symptoms or harm, is an important risk.[1] Comprehensive evaluation of screening programmes acknowledges key biases that include healthy screenee bias, lead or length time biases, and overdiagnosis bias.[1] Ethical concerns include the need for informed consent, as well as impact on health inequalities, if some groups are less able to access screening,[2] and the potential strain on NHS services if the workload of screening worsens access to care for symptomatic patients.

Coeliac disease

Coeliac disease is an autoimmune disorder, triggered by the protein gluten, found in wheat, rye and barley.[3] Eating gluten triggers an abnormal immune response in genetically predisposed individuals (those with human leukocyte antigen (HLA)-DQ2 or DQ8).[4] Gluten peptides increase intestinal permeability and, once across the gut barrier, are modified by tissue transglutaminase (tTG), which enhances their recognition by the immune system.[5] This leads to activation of T cells, production of inflammatory cytokines, and stimulation of intraepithelial lymphocytes, which damage the gut lining.[6] The result is inflammation, villous atrophy, crypt hyperplasia, and malabsorption, which are the hallmark features of coeliac disease.[7]

Coeliac disease has an estimated global prevalence of 1%.[8] Estimates from the UK are generally consistent with this, with studies from Northern Ireland, Nottingham and Sheffield that were conducted in the 1990s and early 2000s reporting a prevalence of 1% in the adult population.[9-11] However, as it can present with a wide range of non-specific symptoms it is

widely underdiagnosed.[12] The HLA-DQ2 or DQ8 risk genotype is required, although not sufficient, to develop coeliac disease.[13]

Although coeliac disease was once thought to be diagnosed predominantly in children, it can develop at any age. It is now most commonly diagnosed between the ages of 40 and 60 (mean age at diagnosis 45 years), and has a higher incidence in women than in men.[14] People with certain risk markers are at an increased risk of having coeliac disease. These include type 1 diabetes, thyroid disease, and having a first degree relative with coeliac disease.[15, 16]

Presentation of coeliac disease

Some patients with coeliac disease may be symptomless, while others present with non-specific symptoms including gastrointestinal symptoms (e.g. diarrhoea, bloating, gassiness, constipation, vomiting, and abdominal pain) and unexplained weight loss.[17] Some adults present with non-gastrointestinal symptoms such as recurrent mouth ulcers, fatigue, dermatitis herpetiformis, migraine, ataxia, seizures, or fertility issues.[18]

Diagnosis of coeliac disease

Diagnosis of coeliac disease usually follows a two-step pathway of serological testing to identify potential coeliac disease, followed by biopsy confirmation of the diagnosis. Genetic testing may also play a role.

Serological testing

Several serological tests are available for coeliac disease: these are summarised in Table 1. All current tests require the patient to consume gluten daily for at least 6 weeks prior to testing. Guidelines for serological testing vary, but most recommend initial testing for immunoglobulin A (IgA) anti-tTG. NICE guidelines recommend follow-up testing with IgA endomysial antibodies (EMA), in those with weakly positive tTG.[19]

Point-of-care/rapid serological tests are also available.[20] These detect either tTG or deamidated gliadin peptide (DGP) antibodies in blood using a finger-prick blood sample, but data on the accuracy of these tests is conflicting.[18, 21] These rapid tests also do not give a numerical result, potentially limiting their usefulness as they cannot show when patients have very high antibody levels making it more likely that they have coeliac disease. However, as there is lack of consensus on thresholds for laboratory based serological tests, with different laboratories also using different tests, this also means that rapid tests could have an important role in a potential screening programme as an initial screening test. These tests are not currently widely used, and it is usually recommended that they are followed by confirmatory standard serological testing.

IgA-based tests are unreliable in IgA-deficient individuals, and so screening for IgA deficiency is advised alongside the initial tTG test. This deficiency affects around 0.5% of the general population and 2 to 3% of those with coeliac disease. If IgA deficiency is present, immunoglobulin G (IgG)-based tests for tTG, DGP or EMA are recommended. Older tests, such as anti-gliadin and anti-reticulin antibodies, are no longer recommended due to inferior accuracy compared to modern assays.

Table 1 Serological tests for coeliac disease

Serological Test	Antibody type	Date available	Test type	Guidelines
Tissue transglutaminase (tTG)	IgA or IgG	1997	Enzyme-linked immunosorbent assay (ELISA).	NICE, ESPGHAN
Endomysial antibody (EMA)	IgA or IgG	~1990	Indirect fluorescent antibody (IFA)	NICE, ESPGHAN
Deamidated gliadin peptide (DGP)	IgA or IgG	1999	ELISA	NICE, ESPGHAN
Rapid test for tTG	IgA	Early 2000	Rapid lateral flow test	Not recommended
Rapid test DGP	IgA or IgG	Early 2000	Rapid lateral flow test	Not recommended
Anti-actin antibodies (AAA)	IgA	~2000	ELISA	Not recommended
Antireculin antibodies	IgA or IgG	1977	IFA (rat kidney)	Not recommended
Antigliadin antibodies (AGA)	IgA or IgG	Early 1980s	Quantitative enzyme immunoassay (EIA)	Not recommended

Abbreviations: NICE = National Institute for Health and Care Excellence, ESPGHAN = European Society for Paediatric Gastroenterology Hepatology and Nutrition, IgA = immunoglobulin A, IgG = immunoglobulin G

Genetic testing

Coeliac disease has a strong genetic component. Nearly all people with coeliac disease carry HLA-DQ2 or DQ8 heterodimers, encoded by HLA-DQA1 and HLA-DQB1 gene variants. Less than 1% of people with coeliac disease lack these markers. However, these markers are also present in around 30 to 40% of the general population, so their presence does not confirm coeliac disease.[16] The role of genetic testing for HLA-DQ2 or DQ8 as part of the diagnostic pathway for coeliac disease is unclear. It is potentially most useful as a "rule-out" test, as absence of these markers makes coeliac disease very unlikely. NICE guidelines advise against its use in initial diagnosis in non-specialist settings but note it may be useful in selected cases, such as in biopsy-free paediatric diagnosis or in individuals already on a gluten-free diet.

Biopsy confirmation

NICE guidelines recommend that biopsy is used to confirm coeliac disease in all adults with positive serology, regardless of antibody levels.[19] Biopsy is invasive, costly, unpleasant and carries risks, especially in children, who usually require general anaesthesia. As with serological tests, patients must eat gluten daily in the 6 weeks prior to biopsy for the result to be reliable. Although serological tests have a quick turnaround (usually 1 to 2 weeks), there are long waiting times for endoscopies required for the biopsy. In 2022, over 200,000 people were on the endoscopy waiting lists in the UK, and only 18% of services were meeting the routine endoscopy waiting time targets.[22]

For children with positive serology, NICE recommends referral to paediatric gastroenterology but does not mandate biopsy. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2012 guidelines allow for a non-biopsy diagnosis in children with IgA tTG ≥10× the upper limit of normal (ULN), positive IgA EMA, and a compatible HLA genotype.[23] In 2018, Finnish guidelines recommended a no-biopsy pathway for adults,[24]

which was temporarily adopted by the British Society of Gastroenterology (BSG) at the start of the Covid-19 pandemic.[25, 26]

Treatment of coeliac disease

The only effective treatment for coeliac disease is strict, lifelong adherence to a gluten-free diet. This may negatively affect quality of life, meaning it is important to be confident that a coeliac disease diagnosis is correct. Adherence to a gluten-free diet can be challenging, particularly in those who are symptomless at diagnosis, who may have less motivation for following a gluten-free diet. Barriers to diet adherence include the cost of obtaining gluten-free products, difficulty in identifying if food is gluten-free, dislike of gluten-free foods or not wanting the hassle of managing one's diet. However, those that strictly follow a gluten-free diet generally report improvements in symptoms, and even those who are considered symptomless at diagnosis often find that they feel better on a gluten-free diet.[27] In a recent survey of 244 people with a diagnosis of coeliac disease, Elwenspoek et al found that 131 (53.5%) respondents found it easy or very easy to follow the gluten-free diet, whereas 69 (28.2%) respondents found it difficult or very difficult.[16] Most respondents with confirmed coeliac disease reported that they were strict or very strict in their adherence to the gluten-free diet (n=222, 90.6%), with only 2% reporting that they were not very strict.[16] Our survey also found that those who found it difficult to follow a gluten-free diet or those that followed a gluten-free diet very strictly reported it to have had a greater impact on quality of life.[28]

New treatments are in the development pathway, but most are still in pre-clinical phases. These aim to allow people with coeliac disease to be able to eat gluten, or experience inadvertent gluten contamination, without becoming symptomatic or damaging the intestinal lining.[29]

There is some evidence that, if left untreated, coeliac disease can cause small intestinal mucosal damage and impaired nutrient absorption, leading to malnutrition, anaemia, and osteoporosis. Long-term untreated coeliac disease is also associated with increased risks of complications, including lymphoma, small bowel carcinoma, and osteoporosis.[30, 31]

Previous reviews and recommendations on screening for coeliac disease

The most recent UK NSC review of screening for coeliac disease was an evidence summary, published in 2014.[33] Evidence summaries (also known as rapid reviews) provide information on the volume, type and direction of evidence on a particular question or set of questions on a given screening topic, considering the quantity, quality, applicability, and consistency of the evidence. The UK NSC currently recommends against screening for coeliac disease. The Committee based this recommendation on the evidence provided by the 2014 evidence summary review carried out by Spiby Health.[33] The last review prior to this was published in 2008.

The 2008 UK NSC review concluded that coeliac disease "did in many ways fulfil the World Health Organisation criteria for screening but the real/actual benefit of population screening remains questionable." This was because of: a lack of knowledge of the natural history of undetected cases of coeliac disease, financial limitations due to lack of support services for

patients after diagnosis and the lack of evidence on whether patients detected through screening programmes would adhere to a gluten-free diet.

The 2014 evidence summary on screening for coeliac disease used a selective criteria format, focussing on areas of the 2008 review where the evidence was insufficient. These included natural history, prevalence, diagnosis, treatment, and services. Key findings of the UK NSC 2014 evidence summary were:

- the clinical course of undiagnosed coeliac disease was still poorly understood
- the evidence supporting the effectiveness of dietary intervention in screen-detected, largely symptomless individuals was limited, with no clear demonstration of health benefits
- there was some evidence suggesting lower adherence to treatment among symptomless individuals than symptomatic individuals
- no UK cost-effectiveness studies were identified, but evidence from a study of US primary care data concluded that screening was not cost-effective (using NICE's upper threshold of £30,000 cost per quality-adjusted life year gained)
- further research was needed to identify the best series of diagnostic tests to confirm a case of coeliac disease, and
- no major UK trials were undertaken between 2008 and 2014

The US Preventative Services Task Force advises against screening for coeliac disease due to insufficient evidence on the benefits and harms of screening. This recommendation is based on a systematic review conducted in 2017, which aimed to assess 7 questions around outcomes associated with screening and treatment, and accuracy of serological tests.[34] The key questions were:

1. What is the effectiveness of screening vs not screening for coeliac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?
2. What is the effectiveness of targeted vs universal screening for coeliac disease in asymptomatic adults, adolescents, or children on morbidity, mortality, or quality of life?
3. What are the harms of screening for coeliac disease?
4. What is the accuracy of screening tests for coeliac disease?
5. Does treatment of screen-detected coeliac disease lead to improved morbidity, mortality, or quality of life compared with no treatment?
6. Does treatment of screen-detected coeliac disease lead to improved morbidity, mortality, of quality of life compared with treatment initiated after clinical diagnosis?
7. What are the harms associated with treatment of coeliac disease?

An additional literature scan was conducted in May 2024 and showed insufficient new evidence to support an updated systematic review.[35]

Aims of the evidence map

The BESS (Bristol Evidence Synthesis for Screening) Group has been commissioned to produce this evidence map. An evidence map is a rapid evidence product which aims to gauge the volume and type of evidence relating to a specific topic.

This evidence map provides a summary of the volume and type of evidence to inform 4 key questions relating to screening for coeliac disease

1. What is the prevalence of coeliac disease in high-risk groups?
2. What is the accuracy of screening tests for coeliac disease?
3. Does screen detection of coeliac disease and intervention provide better health outcomes than treatment of coeliac disease identified through symptoms, known high risk groups or opportunistic testing?
4. What is the effectiveness of targeted versus universal screening for coeliac disease in symptomless adults?

The findings of this evidence map will provide the basis for discussion to support decision-making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on screening for coeliac disease in 2025.

The aim of this document is to present the information necessary to inform UK NSC decision-making processes.

Search methods and results

Detailed methods, including eligibility criteria and search strategies, are available in Appendix 1.

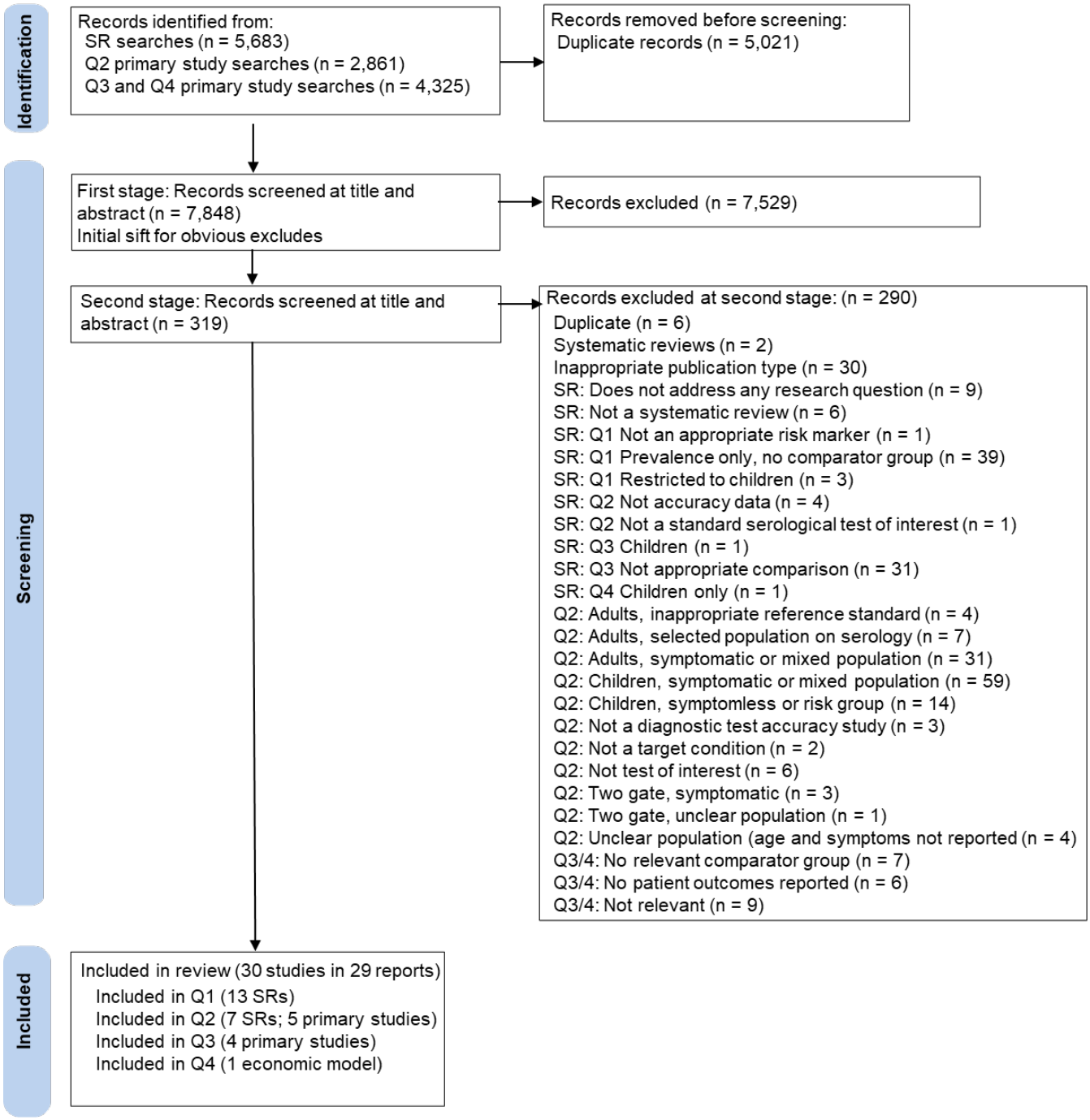
MEDLINE and Embase databases were searched. A two-step approach was utilised, with an initial literature search focused on identifying relevant systematic reviews. This was followed by supplementary searches for primary studies for questions where no directly relevant systematic reviews were found. Supplementary searches were conducted for questions 2, 3 and 4. The search period was restricted to January 2014 to June 2025. Deduplication was conducted automatically using Nested Knowledge® (nested-knowledge.org).

Titles and abstracts were screened by 1 reviewer. A random sample of 20% of records were independently screened by a second reviewer. The remaining 80% were screened using the AI screening model (Robot Reviewer) integrated in Nested Knowledge®. Disagreements between the AI Screening and the human reviewer were resolved by a human reviewer. All references were reviewed at abstract level. As this was an evidence map, only ‘top level’ study information was extracted. Full texts were only reviewed to clarify uncertain pieces of information, for data extraction only. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2. The initial database search to identify systematic reviews returned 5,683 results. After automatic de-duplication, 4,226 unique references were reviewed for relevance to the review questions. The supplementary search to address question 2 retrieved 2,861 results, with 1,956 remaining after automatic deduplication. The supplementary search to address questions 3 and 4 retrieved 4,325 results, with 1,657 remaining after automatic deduplication.

A flow diagram summarising the flow of studies through the evidence map is presented in Figure 1.

Figure 1: PRISMA flow diagram



Summary of findings

Question 1: What is the volume and type of evidence on the prevalence of coeliac disease in high-risk groups?

Thirteen systematic reviews were included for this question (Table 2 and Appendix 2).[15, 36-47] These reviews synthesised studies that compared the prevalence of coeliac disease in groups of participants with and without specific risk markers. Since there is a large body of evidence on prevalence of coeliac disease in different risk groups, we restricted our inclusion criteria to look at comparative evidence (i.e. comparing prevalence in people with and without the risk marker), which we consider more informative due to the varying prevalence of coeliac disease in different populations.

The most comprehensive systematic review, with a search date of April 2021, aimed to identify risk markers that could identify people at higher risk of coeliac disease, for whom further testing may be warranted.[15] This review included 191 studies and identified 18 risk markers. The review estimated the post-test probability (i.e. prevalence) of coeliac disease in those with specific risk markers, assuming a pre-test probability of coeliac disease of 1%, equivalent to the prevalence in the general population. It reported an approximately 2 to 3% prevalence of coeliac disease in people with dermatitis herpetiformis, migraines, anaemia, type 1 diabetes, osteoporosis, liver disease, and having a first degree relative with coeliac disease. There was an estimated 1.5 to 2% prevalence of coeliac disease amongst those with thyroid disease, irritable bowel syndrome and subfertility or recurrent pregnancy loss. The following risk markers were also associated with a 1.5 to 2% prevalence of coeliac disease, but confidence intervals were wider and so the evidence was less certain: psoriasis, epilepsy, inflammatory bowel disease, systemic lupus erythematosus, fractures, and arthritis. There was no evidence for an increased prevalence in those with type 2 diabetes or multiple sclerosis.

The other systematic reviews each focused on a smaller number of specific risk markers and quantified the association between each risk marker and coeliac disease as odds ratios (OR) or relative risks based on the proportion of people with coeliac disease amongst those with and without the risk marker. Three systematic reviews evaluated the prevalence of coeliac disease in those with neurodevelopmental disorders and psychiatric conditions compared to those without.[36-38] One review included autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), bipolar disorder, and schizophrenia.[36] One review focused on autism spectrum disorder,[37] and 1 on Turner syndrome.[38] An increased prevalence of coeliac disease was reported in people with ADHD, bipolar disorder, and Turner syndrome.[37] The evidence was less clear for autism spectrum disorder, with 1 review suggesting an increased prevalence of coeliac disease in people with autism spectrum disorder,[36] and another reporting a potential association between coeliac disease and autism spectrum disorder, based on limited population-based studies.[36, 37] There was no evidence of a difference in the prevalence of coeliac disease in those with schizophrenia versus those without .[36]

Three systematic reviews evaluated the association between infertility and coeliac disease.[39-41] All reported an increased prevalence of coeliac disease in women experiencing infertility. Four systematic reviews evaluated the prevalence of coeliac disease in people with gastrointestinal disorders.[42-45] One review reported an increased prevalence of coeliac disease in those with

inflammatory bowel disease, compared to any control,[43] 1 reported an increased prevalence of coeliac disease in those with inflammatory bowel syndrome compared to healthy controls,[42] 1 reported an increased prevalence of coeliac disease in those with microscopic colitis.[44] The final review found no evidence of an increased prevalence of coeliac disease in those with dyspepsia, compared to controls.[45] Two systematic reviews reported an increased prevalence of coeliac disease in those with psoriasis.[46, 47]

In summary, we identified 13 systematic reviews that evaluated the association between coeliac disease and various potential risk markers by comparing the prevalence of coeliac disease amongst those with and without each risk marker.

There is a large body of evidence available on the prevalence of coeliac disease in those with specific risk markers, compared with control groups without the risk marker. On the basis of the evidence available for this question, further work on screening for coeliac disease may be justified.

Table 2: Overview of systematic reviews that provided evidence on question 1

Review	Risk marker	Search Date	Number of included studies (N = participants)	Results reported in abstract	Test used to diagnose coeliac disease
Mixed risk factors					
Elwenspoek et al (2021)[15]	• Anaemia • Arthritis • Chronic liver disease • Dermatitis herpetiformis • Diabetes • Family history of coeliac disease • Fractures • Infertility • Inflammatory bowel disease • Inflammatory bowel syndrome • Migraine • Multiple sclerosis • Osteoporosis • Psoriasis • Systemic lupus erythematosus • Thyroid disease • Type 2 diabetes	April 2021	191 studies (number of participants not reported in abstract)	Strong evidence for increased prevalence of coeliac disease in people with dermatitis herpetiformis, migraine, family history of coeliac disease, HLA DQ2 or DQ8 risk genotype, anaemia, type 1 diabetes, osteoporosis, or chronic liver disease. 3-fold higher prevalence of coeliac disease in first-degree relatives of coeliac disease patients. Psoriasis, epilepsy, inflammatory bowel disease, systemic lupus erythematosus, fractures, type 2 diabetes, and multiple sclerosis showed no increased prevalence of coeliac disease compared to those with these comorbidities.	Biopsy and/or serology
Neurodevelopmental or psychiatric conditions					
Clappison et al (2020)[36]	• ADHD • Autism spectrum disorder • Bipolar disorder • Schizophrenia	May 2019	37 studies (number of participants not reported in abstract)	OR representing association with coeliac disease by risk factor: • ASD: 1.5 (95% CI 1.2, 1.9,) • ADHD: 1.4 (95% CI 1.2, 1.6) • Bipolar disorder: 2.4 (95% CI 2.3, 19.2) • Schizophrenia: 0.5 (95% CI 0.0, 10.2)	Not reported in abstract

Review	Risk marker	Search Date	Number of included studies (N = participants)	Results reported in abstract	Test used to diagnose coeliac disease
Quan et al (2021)[37]	Autism spectrum disorder	Not reported in abstract	13 studies (number of participants not reported in abstract)	Most studies had small sample sizes and reported no evidence for an association between the 2 conditions. However, a limited number of population-based studies of higher quality suggested a potential association between coeliac disease and ASD (numerical results not reported in abstract)	Not reported in abstract
Al-Bluwi et al (2021)[38]	Turner syndrome	December 2019	4 studies (number of participants not reported in abstract)	Association with coeliac disease: • Study 1, OR: 18.1 (95% CI 1.8, 180) • Study 2, OR: 4.3 (95% CI 1.5, 12.8) • Study 3, RR: 14.0 (95% CI 1.5, 12.8; *note RR falls outside reported CI, likely error)* • Study 4, RR: 42.5 (95% CI 12.4, 144.8)	Not reported in abstract
Reproductive health					
Castano et al (2019)[39]	Infertility	June 2019	23 studies (number of participants not reported in abstract)	Three times higher odds of having coeliac disease in people with infertility when compared to controls	Biopsy and/or serology
Lasa et al (2014)[40]	Infertility	December 2013	12 studies (number of participants not reported in abstract)	Association between coeliac disease and infertility: OR = 3.1 (95% CI 1.7, 5.5)	Not reported in abstract
Singh et al (2016)[41]	Infertility	Not reported	5 studies (number of participants not reported in abstract)	OR for association of coeliac disease with: • Infertility: 3.5 (95% CI 1.3, 9.0). • "Unexplained" infertility: 6.0 (95% CI 2.4, 14.6)	Biopsy and/or serology
Gastrointestinal disorders					
Irvine et al (2017)[42]	Irritable bowel syndrome	May 2016	36 studies (N = 15,256)	OR representing association between coeliac disease and irritable bowel syndrome:	Biopsy and/or serology

Review	Risk marker	Search Date	Number of included studies (N = participants)	Results reported in abstract	Test used to diagnose coeliac disease
				• 3.2 (95% CI 1.6, 6.7; based on positive AGA) • 2.8 (95% CI 1.4, 5.6; based on positive tTG or EMA) • 4.5 (95% CI 2.3, 8.6; based on positive biopsy).	
Pinto-Sanchez et al (2020)[43]	Inflammatory bowel disease	June 2019	65 studies (number of participants not reported in abstract)	Association between coeliac disease and inflammatory bowel disease: RR = 4.0 (95% CI 2.2, 7.0)	Biopsy and/or serology
Nimri et al (2022)[44]	Microscopic colitis	January 2022	26 studies (N = 22,802)	• Association between coeliac disease and microscopic colitis: OR = 8.276 (95% CI 5.888, 11.632, p < 0.001 • Prevalence of coeliac disease in microscopic colitis patients: 6.1% (95% CI 3.9%, 9.5%, p < 0.001). • Prevalence of coeliac disease in people with collagenous colitis: 5.2% (95% CI 2.2%, 12.1%, p < 0.001) • Prevalence of coeliac disease in people with lymphocytic colitis: 6.3% (95% CI 3.4%, 11.5%, p < 0.001)	Not reported in abstract
Singh et al (2022)[45]	Dyspepsia	May 2021	21 studies (N = 10,275)	Association between coeliac disease with dyspepsia based on • Serology: OR = 1.8 (95% CI 0.8, 4.0; I^2 = 0%) • Biopsy: OR = 1.4 (95% CI 0.8, 2.4; I^2 = 0%)	Biopsy and/or serology
Psoriasis					
Acharya et al (2020)[46]	Psoriasis	Not reported in abstract	18 studies; 9 included in meta-analysis (number of participants not	Association between coeliac disease and psoriasis: OR = 2.2 (95% CI 1.7, 2.7)	Not reported in abstract

Review	Risk marker	Search Date	Number of included studies (N = participants)	Results reported in abstract	Test used to diagnose coeliac disease
			reported in abstract)		
Ungprasert et al (2017)[47]	Psoriasis	Not reported in abstract	4 studies (2,912 cases of psoriasis and 24,739 comparators)	Association between coeliac disease and psoriasis: OR = 3.1 (95% CI 1.9, 5.0)	Not reported in abstract

Abbreviations: ADHD = attention deficient hyperactivity disorder, AGA = anti-gliadin antibodies, ASD = autism spectrum disorder, CI = confidence intervals, EMA = endomysial antibodies, HLA = human leukocyte antigen, OR = odds ratio, RR = risk ratio, tTG = tissue transglutaminase

Question 2: What is the volume and type of evidence on the accuracy of screening tests for coeliac disease?

Seven systematic reviews were included for this question, but none of these focused specifically on a general symptomless (screening) population (Table 3 and Appendix 2).[16, 20, 34, 48-51]

Two systematic reviews assessed the accuracy of standard laboratory-based serological tests.[34, 48] The most comprehensive systematic review included 113 studies conducted in adults and children, with 5 included in the meta-analysis for the accuracy of tests in adults.[48] None of the included studies were conducted in a symptomless population. In this review, tTG and EMA were evaluated against the reference standard of duodenal biopsy. Summary sensitivity and specificity of tTG tests were reported as 91% (95% CI 87, 93) and 87% (95% CI 84, 90) respectively. The summary sensitivity and specificity of EMA tests were reported as 88% (95% CI 75, 95) and 100% (95% CI 92, 100), respectively. The other systematic review, a report commissioned by the US Preventive Services Task Force to evaluate the potential for screening for coeliac disease, included 1 recent systematic review, 12 previous systematic reviews, and 2 primary diagnostic test accuracy studies.[34] This review reported that the sensitivity and specificity of tTG were >90%. Only 1 study included in the systematic review included a symptomless adult population, although this population was at increased risk of coeliac disease as participants had type 1 diabetes mellitus. Sensitivity of tTG was lower in this study (71% for IgA tTG and 57% for IgG tTG), but specificity remained high (98% for IgA tTG and 93% for IgG tTG), compared with the summary estimates from the meta-analysis.

One systematic review evaluated the accuracy of a no-biopsy strategy compared to duodenal biopsy.[49] The no-biopsy strategy utilises a very high threshold of IgA tTG to rule in coeliac disease, to investigate whether biopsies could be avoided in those with very high test results (at least 10x the upper limit of normal (ULN)). Summary specificity was 100% (95% CI 98,100), suggesting that a no-biopsy strategy could be used for ruling in coeliac disease in people with very high tTG levels. Although sensitivity was lower (51%; 95% CI 42, 60), this threshold would not be used to rule out a diagnosis of coeliac disease. Those with test results between 1 and 10× the ULN would receive a biopsy to confirm or rule out the diagnosis.

One review evaluated the accuracy of a novel laboratory method (CLIA-assay), using a reference standard of a tTG-based strategy and duodenal biopsy.[50] The review included 11 studies, with 7 included in the meta-analysis. The estimated summary sensitivity and specificity for the method were 98% (95% CI 95, 99) and 97% (95% CI 94, 99) respectively.

One review evaluated the accuracy of point-of-care tests (including tTG, tTG plus AGA, and DGP). For all point-of-care tests combined, sensitivity was estimated as 94% (95% CI 90, 97) and specificity as 94% (95% CI 91, 97). The sensitivity and specificity of tTG-based point of care tests were 91% (95% CI 82, 95) and 95% (95% CI 93, 96), respectively. It was unclear from the abstract how many studies were included and whether the reference standards used in the included studies consisted of standard laboratory-based serology or biopsy.

Two reviews evaluated the accuracy of tests for the genetic markers HLA DQ2 or DQ8 as tests for diagnosing coeliac disease.[16, 51] The reviews reported high summary sensitivity of 98% (95% CI 97, 99) and 99% (95% CI 83, 100), with lower summary specificity of 45% (95% CI 41, 48) and 56% (95% CI 50, 61).

Due to a lack of systematic reviews in symptomless populations, we conducted additional searches to identify primary studies conducted in symptomless populations — either a general

screening population or in those with specific risk markers. A total of 5 one-gate (also known as diagnostic cohort or cross-sectional) diagnostic test accuracy studies were identified.[52-56] These are summarised in Table 4. Duodenal biopsy was used as the reference standard in each of these studies. However, only one of these five studies reported any accuracy measures other than the positive predictive value (PPV).

Two studies evaluated the accuracy of tests for coeliac disease in the adult general population.[52, 54] Despite the low estimated prevalence of coeliac disease in these studies (<1%), they reported high summary positive predictive values (PPVs) for IgA tTG in symptomless adults, at 73% and 88% respectively. However, symptomless adults with normal screening results did not undergo confirmatory testing in either study. This means that data were not available to allow calculation of prevalence, sensitivity, specificity, or negative predictive value.

The remaining 3 studies assessed the accuracy of no-biopsy diagnostic strategies compared to duodenal biopsy in mixed populations, including individuals at familial risk for coeliac disease, those with clinical indications, and low-risk groups.[53, 55, 56] Overall, these studies found that tTG testing at high thresholds (≥10× the ULN), demonstrated a high PPV, supporting its use for ruling in coeliac disease. One study also provided data on sensitivity and specificity. It reported that, at high thresholds (≥10× the ULN), specificity was high. Sensitivity was low (50%) but, as in the systematic reviews of the no-biopsy strategy, this threshold would not be used to rule out coeliac disease.[55]

Appendix 3 presents additional relevant evidence from conference abstracts that were relevant to this question but were not included in this evidence map, as conference abstracts are not eligible for evidence maps.

Overall, there was little evidence from screening populations, including those with specific risk markers. We found that there is a large body of evidence quantifying the accuracy of serological tests in symptomatic populations. This suggests that serological tests have good accuracy in this population. Limited evidence suggests that the PPV is high in screening and risk populations, despite a low pre-test probability of disease. Based on the current evidence, commissioning an evidence summary on the accuracy of screening strategies for coeliac disease may be warranted. This could provide a more in-depth synthesis of studies in screening populations and those with specific risk markers. As the evidence map suggests limited data in these groups, an evidence review could also investigate whether there is evidence to suggest that the accuracy of serological tests for coeliac disease varies with the prevalence of disease in the study populations.

Table 3: Overview of systematic reviews that provided evidence on question 2

Review	Search Date	Number of included studies (N = participants)	Reference standard	Index test(s)	Summary sensitivity (%, 95% CI)	Summary specificity (%, 95% CI)
Standard laboratory based serological tests						
Sheppard et al* (2022)[48]	August 2020	113 studies (N = 28,338), 5 included in meta-analysis	Duodenal biopsy	tTG	90.7 (87.3, 93.2)	87.4 (84.4, 90.0)
				EMA	88.0 (75.2, 94.7)	99.6 (92.3, 100.0)
Chou et al (2017)[34]	June 2016	1 recent systematic review of 56 studies (number of participants not reported in abstract), 12 previous systematic reviews (N = 62 to 12,000) and 2 diagnostic test accuracy studies (N = not reported in abstract)	Not reported in abstract	tTG	Only 1 study in a symptomless adult population and reported lower sensitivity (IgG: 57% and IgA: 71%), specificity remained > 90%.	
				EMA	Not reported in abstract	EMA associated with high specificity.
No biopsy strategy						
Shiha et al (2024)[49]	October 2023	18 studies (N = 12,103) Prevalence of coeliac disease 62% (95% CI 40%, 83%).	Duodenal biopsy	IgA tTG ≥10^{x}ULN (no biopsy strategy)	51 (42, 60)	100 (98, 100)
Novel laboratory method (CLIA-assay)						
Pjetraj et al (2024)[50]	March 2024	11 studies; 7 were included in meta-analysis (number of participants not reported in abstract)	tTG based strategy; Duodenal biopsy	IgA tTG CLIA-assay	98 (95, 99)	97 (94, 99)
POCT tests						
Singh et al (2019)[20]	July 2017	Not reported in abstract	Not reported in abstract	All POCT (tTG, tTG plus AGA; DGP)	94.0 (89.9, 96.4)	94.4 (90.9, 96.5)
				tTG based POCT	90.5 (82.3, 95.1)	94.8 (92.5, 96.4)
HLA tests						
Diaz-Redondo et al (2015)[51]	December 2013	6 studies (N = 1,303)	Not reported in abstract	HLA DQ2 or DQ8	98 (97, 99)	45 (41, 48)
Elwenspoek et al (2022)[16]	August 2020	4 studies (N = 12,087)	Not reported in abstract	HLA DQ2 or DQ8	99.2 (83.4, 100.0)	55.6 (50.2, 60.9).

*Results reported only for adults; data also available for children and for other serological tests (results for these not available in abstract)

Table 4: Overview of diagnostic test accuracy studies that provided evidence on question 2

Study and location	Relevant population	Number of participants	Number of cases	Reference standard	Index test(s)	Results reported in abstract
Standard threshold						
Andersen et al (2025)[52] Norway	Screening population	56,042	423 (Prevalence = 0.8%)	Duodenal biopsy (in seropositive individuals only)	Dual assay to assess IgA and IgG tTG together	PPV by test: • tTG IgA positive: 73.3% (95% CI 69.7%, 77.0%) • tTG IgA-negative, IgG positive: 5.8% (95% CI 1.9, 12.9%)
Karhus et al (2016)[54] Denmark	Screening population	2,297	8 (Prevalence = 0.3%)	Duodenal biopsy (in seropositive individuals only)	IgA tTG	IgA tTG with a cut-off of 10 U/ml had a PPV of 88%
No biopsy strategy						
Fuchs et al (2019)[53] Finland	Low-risk subjects from the general population; Family members of people with coeliac disease	2,722 low-risk subjects 2,357 family members,	85 family members (3.6%), 29 low risk subjects (1.1%)	Duodenal biopsy	tTG antibodies ≥10× ULN, positive EMA, and HLA-DQ2 or DQ8	In participants positive on the triple criteria for diagnosis, the PPV was 100%
Penny et al (2021)[55] UK	Participants with low clinical suspicion referred for endoscopy (UK) and participants with elevated tTG from international sites	Low clinical suspicion: 532	Not reported in abstract	Duodenal biopsy	IgA tTG	Low clinical suspicion: • Sensitivity: 50.0% • Specificity: 100.0% • PPV: 100.0% • NPV: 98.3%
Ylonen et al (2020)[56] Finland	Family members of people with coeliac disease	836 overall, (number with family risk not reported in abstract)	85 cases with family risk	Duodenal biopsy	IgA tTG 10× the ULN and positive EMA	In participants positive for IgA tTG 10× ULN and positive EMA, the PPV was 100%. Using the assays' own cut-offs (1× ULN) the PPVs ranged 84 to 100% (PPV for cases with family risk not reported separately in abstract from overall cohort)

Abbreviations: EMA = endomysial antibodies, HLA = human leukocyte antigen, IgA = immunoglobulin A, IgG = immunoglobulin G, NPV = negative predictive value, PPV = positive predictive value, tTG = tissue transglutaminase, ULN = upper limit of normal,

Question 3: What is the volume and type of evidence available that demonstrates whether screen detection of coeliac disease and intervention provide better health outcomes than treatment of coeliac disease identified through symptoms, known high risk groups or opportunistic testing?

No systematic reviews were identified through our initial search that directly fulfilled the inclusion criteria for this review question. We therefore conducted additional targeted searches to identify primary studies which included participants with screen-detected coeliac disease. Due to capacity constraints, additional searches were not performed for other population groups specified in the protocol. We identified 4 studies that fulfilled inclusion criteria for this question (Table 5).[63-66]

Three studies compared outcomes between individuals with screen-detected coeliac disease and those diagnosed based on symptomatic presentation. Across these studies, adherence to a gluten-free diet and general health outcomes were broadly similar between the 2 groups, although 1 study with a small sample size (59 cases) suggested slightly lower gluten-free diet adherence among those diagnosed through screening.[63] One study reported that screen-detected individuals were less likely to have osteopenia or osteoporosis at the time of diagnosis compared to those diagnosed based on symptoms.[64] Another study found that individuals diagnosed through screening during childhood reported higher levels of anxiety than those diagnosed after presenting with symptoms.[63, 65]

A prospective open-label randomised controlled trial investigated the effects of a gluten-free diet in adults with type 1 diabetes who were newly diagnosed with coeliac disease through screening.[66] Thirty participants were randomised to either a gluten-free or gluten-containing diet for 6 months. The study reported a reduction in the number of hypoglycaemic episodes from baseline to 6 month follow up in the gluten-free diet group. However, the sample size was small.

We identified additional potential study types that could be considered to help answer this question based on our search for systematic reviews (Appendix 3).

Overall, there was some evidence to suggest that people with screen detected coeliac disease have improved outcomes compared to those detected based on symptomatic presentation. Based on the current evidence, commissioning an evidence summary of the effects of screen detection or detection through symptoms of coeliac disease on associated outcomes may be warranted.

Table 5: Overview of primary studies that fulfilled inclusion criteria for question 3

Study and location	Study type	Study size	Follow up	Results reported in abstract
Adults in the general population: screen detected vs detection based on symptoms				
Cozzi et al (2022)[63] Italy	Cross-sectional (comparative)	59 cases (25 screen detected, 35 symptom detected)	20 years	• Adherence to gluten-free diet after 20 years was optimal in 14 (56%), improvable in 5 (20%) and inadequate in 6 (24%) of those diagnosed with screening • Adherence to a gluten-free diet in those diagnosed for symptoms was optimal in 26 (81%), improvable in 3 (9%) and inadequate in 3 (9%) • Development of other autoimmune diseases was reported in 4 (16%) and 6 (18%) cases detected through screening and by symptoms, respectively
Kivela et al (2018) [64] Finland	Cross-sectional (comparative)	236 cases (48 screen detected, 188 symptom detected)	Patients completed the questionnaires a median of 18.5 years after childhood diagnosis of coeliac disease	• Screen-detected patients had coeliac disease in the family and type 1 diabetes more often, and were less often smokers and members of coeliac societies compared to clinically detected patients • The groups did not differ in current self-experienced health or health concerns, quality of life or dietary adherence • Screen-detected, originally symptomless patients had more anxiety than those presenting with symptoms
Tovoli et al (2018) [65] Italy	Cross-sectional (comparative)	750 cases (number of participants in screen detected versus symptom detected groups not reported in abstract)	Not reported in abstract	• The groups shared a similar adherence to the gluten-free diet (91.2 versus 89.8%, $p = 0.857$). Moreover, the rates of non-responsive coeliac disease, gluten-free-diet-induced metabolic alterations, and persistence in controls were also similar. • Screening-detected patients had a significantly lower rate of osteopenia/osteoporosis at diagnosis (31.3 versus 46%, $p < 0.001$)
Symptomless adults with coeliac disease: comparison of those following and not following a gluten-free diet				

Study and location	Study type	Study size	Follow up	Results reported in abstract
Kaur et al (2020) [66] India	Prospective open label RCT	30 adults with screen-detected coeliac disease (15 on GFD, 15 on gluten-containing diet	6 months	• The mean number of hypoglycaemic episodes per month was 2.3 episodes in the gluten-free diet group and 3.4 episodes in the gluten containing diet group (p = 0.5). • The mean number of hypoglycaemic episodes was 3.5 episodes per month at baseline and 2.4 episodes per month at 6 months (p = 0.03), in the gluten-free diet group. • The mean time spent in hypoglycaemia was 124.1 minutes in the gluten-free diet group compared to 356.9 minutes in the gluten containing diet group (p = 0.1). • Mean HbA1c declined by 0.73% in the gluten-free diet group from baseline to 6 month follow-up, but increased by 0.99% in the gluten containing diet group over the same period.

Question 4: What is the volume and type of evidence on the effectiveness of targeted versus universal screening for coeliac disease in symptomless adults?

No systematic reviews were identified in the initial search. We therefore ran an additional search to identify primary studies reporting outcomes of targeted versus universal screening for coeliac disease in symptomless adults. This identified an economic model comparing different strategies for screening for coeliac disease based on different pre-test probabilities of disease.[16]. These scenarios can be considered to represent targeted screening of different risk groups, based on pre-test probabilities. The scenarios considered also included a 1% pre-test probability, which is equivalent to universal population screening, given the estimated prevalence of coeliac disease in the general population. This economic model was part of a larger project. One of the systematic reviews included for research question 1 (risk markers for coeliac disease) and 2 of the reviews included for question 2 (accuracy of serological and genetic tests for coeliac disease) were used to inform the model.[15, 16, 48]

The cost-effectiveness analysis suggested that population-based screening for coeliac disease in adults - testing men and women with a 1% pre-test probability using serological tests - had the highest net benefit at a threshold of £20,000 per quality-adjusted life-year, with incremental net benefits of around £24,000 compared to no screening. Strategies using both HLA and serological testing with pre-test probabilities of 1–20% had very similar net benefits to each other and to those of IgA tTG testing with 1% pre-test probability, and 95% CIs were completely overlapping. However, the authors highlighted that there was substantial uncertainty in these results and that decisions about implementing a screening programme should not rely on this analysis alone.

In summary, we identified only 1 study to address this research question. Whilst this study was directly relevant to the research question it is based on economic modelling rather than a direct comparison of outcomes in populations who have targeted or universal screening programmes. On the basis of the evidence available for this question, a more in-depth review of this economic model may help inform recommendations regarding screening for coeliac disease.

Conclusions

We identified some evidence for each review question. Thirteen relevant systematic reviews were identified for question 1: these provided evidence on the prevalence of coeliac disease in those with specific risk markers compared with control groups without the risk marker. There is sufficient evidence to warrant further evidence synthesis work.

For question 2, we identified 7 systematic reviews which provided evidence on the accuracy of serological tests for coeliac disease. These primarily included symptomatic populations. We identified 5 additional primary studies conducted in symptomless populations or those with specific risk markers. Although detailed data extraction and assessment of quality of these studies was beyond the scope of this evidence map, data presented in the abstracts suggest that serological tests have high accuracy in symptomatic populations. There is less information in screening populations, including those with specific risk markers, but limited evidence from study abstracts suggests that the PPV remains high in these populations, despite a low pre-test probability of disease.

We identified less evidence for question 3. Four primary studies, conducted specifically in screening populations, were identified. No systematic reviews fully met our inclusion criteria, although we identified 8 systematic reviews that provided evidence that could help answer this question. Overall, there was sufficient evidence to conduct further evidence synthesis work to evaluate the benefits of screen detection and treatment of coeliac disease.

We identified only 1 relevant study addressing question 4. Whilst this study was directly relevant to the research question, it is based on economic modelling rather than a direct comparison of outcomes in populations who have targeted or universal screening programmes.

Recommendations

Based on the evidence identified by this evidence map, commissioning an evidence summary to investigate these 4 research questions is justified.

There is substantial evidence on specific risk groups in which coeliac disease may be more prevalent and that could be considered for targeted screening programmes.

A more in-depth investigation of studies on the accuracy of serological tests for coeliac disease in screening populations and those with specific risk markers could help understand whether the high accuracy reported in symptomatic populations is likely to also apply to symptomless populations. If insufficient data are available specifically in screening populations, an evidence summary could consider whether there is any evidence to suggest that accuracy of these tests varies across different study populations.

Whilst we identified limited evidence on whether screen detection of coeliac disease leads to improved outcomes, we did find some relevant studies, and further review of these could help answer this question. Inclusion criteria for an evidence review could be expanded to include studies that measure markers at diagnosis and after a period on the gluten-free diet to investigate whether outcomes improve.

A more in-depth review of the included economic model may provide further evidence on the cost-effectiveness of population-based screening for coeliac disease.

Declaration of interests

Penny Whiting has a son with CD. Debbie Lane has a son, husband and father with CD. Shona Kirtley has a mother and nephew-in-law with CD.

Some members of the BESS Group conducted a systematic review and economic model on optimal case-finding for CD that was published in 2022.[15, 16, 76]

Appendix 1 — Search strategies for the evidence map

MEDLINE Searches

Search for systematic reviews

Database, version and platform

MEDLINE(R) ALL 1946 to May 29, 2025 via OvidSP.

Search date

3 June 2025.

Search filter

Modified version of the McMaster Reviews Search Hedge Best balance of sensitivity and specificity (https://hiruweb.mcmaster.ca/hkr/hedges/).

#	Search terms	Hits
1	Celiac Disease/	22773
2	c?eliac$.ti,kf.	21906
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	956
4	or/1-3	29407
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	10073
6	4 not 5	26073
7	meta analysis.mp,pt.	340246
8	(metaanaly$ or meta-analy$ or "meta analysis" or metanal$).ti,ab.	347793
9	(review or search$).ti,ab.	2861922
10	(review or systematic review).pt.	3627041
11	or/7-10	4799900
12	6 and 11	4478
13	(exp animals/ not humans.sh.)	5342254
14	12 not 13	4468
15	english.lg.	34020389
16	14 and 15	3870
17	limit 16 to yr="2014-2025"	2022

Supplementary primary study search for question 2

Database, version and platform

MEDLINE(R) ALL 1946 to June 11, 2025 via OVIDSP.

Search date

12 June 2025.

Search strategy

Modified version of the MEDLINE search strategy used in: Sheppard AL, Elwenspoek MMC, Scott LJ, Corfield V, Everitt H, Gillett PM, Hay AD, Jones HE, Mallett S, Watson J, Whiting PF. Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease. Aliment Pharmacol Ther 2022;55(5):514-527.

#	Search terms	Hits
1	Celiac Disease/	22792
2	c?eliac$.ti,kf.	21941
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	956
4	or/1-3	29445
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	10087
6	4 not 5	26103
7	Serologic Tests/	22014
8	((serologic or serological) adj4 test*).tw,kf.	26091
9	7 or 8	44553
10	((antibod* or immunoglobulin* or IgG or IgA) adj4 (endomysi* or EMA)).tw,kf.	1712
11	((antibod* or immunoglobulin* or IgG or IgA) and (anti-endomysi* or anti endomysi* or antiendomysi*)).tw,kf.	1108
12	anti-EMA.tw,kf.	124
13	or/10-12	2134
14	transglutaminases/ or protein glutamine gamma glutamyltransferase 2/	7701
15	((antibod* or immunoglobulin* or IgG or IgA) adj4 transglutaminase*).tw,kf.	2314
16	((anti-tissue or anti tissue or antitissue) and transglutaminase*).tw,kf.	936
17	((anti-human or anti human or antihuman) and transglutaminase*).tw,kf.	59
18	((tissue adj4 transglutaminase*) and (antibod* or immunoglobulin* or IgG or IgA)).tw,kf.	2120

#	Search terms	Hits
19	(anti-httg or anti-htg or tTg).tw,kf.	2644
20	or/14-19	10262
21	((antibod* or immunoglobulin* or IgG or IgA) and (deamidated gliadin peptide* or DGP)).tw,kf.	293
22	(anti-deamidated gliadin peptide* or anti-DGP).tw,kf.	107
23	21 or 22	294
24	9 or 13 or 20 or 23	55340
25	6 and 24	4314
26	exp animals/ not humans.sh.	5347176
27	exp Animals, Laboratory/	1000479
28	exp Animal Experimentation/	10717
29	exp Models, Animal/	684305
30	((animal model* or mouse or mice or murine* or rat or rats or rodent* or muridae or murids or rabbit* or leporine* or leporidae or guineapig* or cavies or caviidae or hamster* or cricetidae or gerbil* or gerbillinae or cat or cats or feline* or felidae or dog or dogs or canine* or canidae or pig or pigs or piglet* or minipig* or swine* or porcine* or suidae or horse or horses or donkey or donkies or burros or asses or equine* or equidae or sheep or lamb or lambs or ovine or ovidae or goat or goats or cow or cows or cattle or bovine* or bovidae or primate* or monkey or monkeys or macaque or macaques or marmoset or marmosets) not human*).ti.	2532282
31	or/26-30	6091066
32	25 not 31	4236
33	((Celiac Disease/ and Autoantibodies/) or Celiac Disease/di or ((celiac or coeliac) and (disease* or syndrome) and diagnos*).ti,kf.) and (("no" or without or with-out) adj3 biops*).tw,kf.	160
34	33 not 31	160
35	32 or 34	4284
36	(2020 Aug* or 2020 Sep* or 2020 Oct* or 2020 Nov* or 2020 Dec*).dp.	303788
37	(202008* or 202009* or 202010* or 202011* or 202012*).ez,dt,ep.	703192
38	(2021* or 2022* or 2023* or 2024* or 2025*).dp,ez,dt,ep.	7305526
39	36 or 37 or 38	7830386
40	35 and 39	726

Supplementary primary study search for questions 3 and 4

Database, version and platform

MEDLINE(R) ALL 1946 to June 16, 2025 via OVIDSP.

Search date

17 June 2025.

#	Search terms	Hits
1	Celiac Disease/	22796
2	c?eliac$.ti,kf.	21961
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	956
4	or/1-3	29465
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	10093
6	4 not 5	26120
7	Mass Screening/	121861
8	(screen$ or detect$).ti,ab,kf.	3971067
9	7 or 8	3997014
10	6 and 9	4701
11	english.lg.	34107263
12	10 and 11	4351
13	(case report or clinical conference or comment or congress or editorial or historical article or letter or news or newspaper article).pt.	2979592
14	12 not 13	4148
15	limit 14 to yr="2014-2025"	1821

Embase Searches

Search for systematic reviews

Database, version and platform

Embase 1974 to 2025 May 30 via OvidSP.

Search date

3 June 2025.

Search filter

Modified version of the McMaster Reviews Search Hedge Best balance of sensitivity and specificity (https://hiruweb.mcmaster.ca/hkr/hedges/).

#	Search terms	Hits
1	Celiac Disease/	40254
2	c?eliac$.ti,kf.	29686
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	1114
4	or/1-3	45944
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	16335
6	4 not 5	42011
7	meta-analys:.mp.	540568
8	search:.tw.	953715
9	review.pt.	3378204
10	systematic review/ or review/	3452531
11	meta analysis/	359037
12	"systematic review$".ti,ab.	449797
13	or/7-12	4429297
14	6 and 13	6992
15	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or feline or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1313752
16	Animal experiment/ not (human experiment/ or human/)	2763049
17	15 or 16	2845457
18	14 not 17	6981
19	english.lg.	38950016

#	Search terms	Hits
20	18 and 19	6234
21	limit 20 to yr="2014-2025"	3661

Supplementary primary study search for question 2

Database, version and platform

Embase 1974 to 2025 June 11 via OVIDSP.

Search date

12 June 2025.

Search strategy

Modified version of the EMBASE search strategy used in: Sheppard AL, Elwenspoek MMC, Scott LJ, Corfield V, Everitt H, Gillett PM, Hay AD, Jones HE, Mallett S, Watson J, Whiting PF. Systematic review with meta-analysis: the accuracy of serological tests to support the diagnosis of coeliac disease. Aliment Pharmacol Ther 2022;55(5):514-527.

#	Search terms	Hits
1	Celiac Disease/	40371
2	c?eliac$.ti,kf.	29795
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	1115
4	or/1-3	46083
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	16371
6	4 not 5	42135
7	*serology/	9692
8	((serologic or serological) adj4 test*).tw,kf.	35363
9	*serodiagnosis/	9375
10	or/7-9	51452
11	endomysium antibody/	2815
12	((antibod* or immunoglobulin* or IgG or IgA) adj4 (endomysi* or EMA)).tw,kf.	2892
13	((antibod* or immunoglobulin* or IgG or IgA) and (anti-endomysi* or anti endomysi* or antiendomysi*)).tw,kf.	1763
14	anti-EMA.tw,kf.	176

#	Search terms	Hits
15	or/11-14	4533
16	*protein glutamine gamma glutamyltransferase/ec [endogenous compound]	1648
17	protein glutamine gamma glutamyltransferase antibody/	3942
18	((antibod* or immunoglobulin* or IgG or IgA) adj4 transglutaminase*).tw,kf.	4491
19	((anti-tissue or anti tissue or antitissue) adj4 transglutaminase*).tw,kf.	1734
20	((anti-human or anti human or antihuman) and transglutaminase*).tw,kf.	96
21	(tissue adj4 transglutaminase* adj4 (antibod* or immunoglobulin* or IgG or IgA or test* or assay or ELISA)).tw,kf.	3415
22	(anti-httg or anti-htg or tTg).tw,kf.	4789
23	or/16-22	10399
24	((antibod* or immunoglobulin* or IgG or IgA) and (deamidated gliadin peptide* or DGP)).tw,kf.	680
25	(anti-deamidated gliadin peptide* or anti-DGP).tw,kf.	206
26	24 or 25	683
27	10 or 15 or 23 or 26	62806
28	6 and 27	8680
29	(animal/ or nonhuman/) not human/	6949235
30	exp animal experiment/ not human/	2755549
31	exp animal model/ not human/	1443595
32	exp experimental animal/ not human/	654612
33	((animal model* or mouse or mice or murine* or rat or rats or rodent* or muridae or murids or rabbit* or leporine* or leporidae or guineapig* or cavies or caviidae or hamster* or cricetidae or gerbil* or gerbillinae or cat or cats or feline* or felidae or dog or dogs or canine* or canidae or pig or pigs or piglet* or minipig* or swine* or porcine* or suidae or horse or horses or donkey or donkies or burros or asses or equine* or equidae or sheep or lamb or lambs or ovine or ovidae or goat or goats or cow or cows or cattle or bovine* or bovidae or primate* or monkey or monkeys or macaque or macaques or marmoset or marmosets) not human*).ti.	2714199
34	or/29-33	7803518
35	28 not 34	8603
36	*celiac disease/di and "no biopsy".mp.	40
37	36 not 34	40
38	35 or 37	8613
39	(2020* or 2021* or 2022* or 2023* or 2024* or 2025*).yr,dc,dd,dp.	11524002
40	38 and 39	2135

Supplementary primary study search for questions 3 and 4

Database, version and platform

Embase 1974 to 2025 June 16 via OVIDSP.

Search date

17 June 2025.

#	Search terms	Hits
1	Celiac Disease/	40539
2	c?eliac$.ti,kf.	29918
3	("gluten enteropath$" or "gluten-sensitive enteropath$" or "gluten sensitive enteropath$" or "gluten induced enteropath$" or "gluten-induced enteropath$" or "gluten intolerance$" or "celiac sprue" or "nontropical sprue" or "non-tropical sprue").ti,kw.	1118
4	or/1-3	46259
5	(c?eliac adj (angiograp$ or arter$ or axis or plexus or trunk)).ti,ab,kw,hw.	16400
6	4 not 5	42303
7	mass screening/ or screening/	274344
8	(screen$ or detect$).ti,ab,kf.	5247725
9	7 or 8	5287154
10	6 and 9	9503
11	english.lg.	39122584
12	10 and 11	8864
13	(Conference Abstract or Conference Paper or Conference Review or Editorial or Letter or Note).pt.	9511963
14	(Clinical Trials Repository or Conference Proceeding).su.	537792
15	13 or 14	10045616
16	12 not 15	5250
17	limit 16 to yr="2014-2025"	2504

Inclusions and Exclusions

Evidence for all questions was restricted to full reports available in English reported from the 1 January 2014 to June 2025. Conference abstracts, commentaries and editorials were not included. Systematic reviews were eligible for all questions and were included if they fulfilled all review inclusion criteria for any specific question.

Inclusion criteria for each question are summarised below:

Question 1: What is the prevalence of coeliac disease in high-risk groups?

Population	Adults representative of the general population.
Exposure	Any potential risk marker that may help clinicians identify patients for whom further testing for coeliac disease is warranted.
Comparator	Absence of the specific risk marker. If no studies with a comparator group are identified then studies conducted only in people with the specific risk marker will be eligible.
Outcome	Coeliac disease diagnosed by one or more serological tests and/or duodenal biopsy. Studies will be required to report sufficient data to create a 2x2 table cross-tabulating the presence or absence of the risk marker with the presence or absence of coeliac disease.
Study designs	Cohort or case-control studies.

Question 2: What is the accuracy of screening tests for coeliac disease?

Population	Adults representative of the general (screening) population. If no studies in screening populations are found, studies in symptomless patients at higher risk of coeliac disease (e.g. those with diabetes or with a family member with coeliac disease) or in symptomatic populations will also be eligible.
Index test	Any serological or genetic screening tests for coeliac disease, used in isolation or in combination, specifically: • tTG (IgA or IgG) • EMA (IgA or IgG) • DGP (IgA or IgG) • HLA DQ2 or DQ8 Both laboratory and near-patient/rapid tests will be eligible
Reference standard	Duodenal biopsy or a strategy based on a non-biopsy pathway in those with tTG ≥10× the upper limit of normal (ULN) and biopsy in those with lower tTG levels.
Target condition	Coeliac disease
Outcomes	Any measure of accuracy (e.g. sensitivity, specificity, positive predictive values, negative predictive values, likelihood ratios)
Study designs	One gate test accuracy studies in which at least a proportion of those who test negative on the index test also undergo the reference standard.

Question 3: Does screen detection of coeliac disease and intervention provide better health outcomes than treatment of coeliac disease identified through symptoms, known high risk groups or opportunistic testing?

Identifying evidence to address this question is challenging. We consider there to be 3 categories of study that could provide information to help answer this question. This includes studies that compare outcomes between:

1. General populations where screening is offered, followed by intervention (recommendation of gluten-free diet) in those screen-detected and those where diagnosis and treatment is based only on symptomatic presentation
2. Symptomless (or screen detected) adults with coeliac disease recommended to follow a gluten-free diet and symptomatic adults or those diagnosed with coeliac disease based on risk markers or opportunistic testing recommended to follow a gluten-free diet
3. Symptomless adults with coeliac disease that follow a gluten-free diet and symptomless adults with coeliac disease that do not follow the diet

Study category	a	b	c
Population	Adults in the general population	Adults with coeliac disease recommended to follow a gluten-free diet	Symptomless adults with coeliac disease
Intervention/ Exposure	Offering of population screening	Symptomless, or screen-detected coeliac disease	Gluten free diet
Comparator	No offer of screening	Coeliac disease identified through symptoms, known high risk groups or opportunistic testing	Gluten containing diet
Outcomes	• Morbidity (including outcomes related to nutritional deficiencies, such as symptomatic or severe anaemia [i.e., requiring treatment], osteoporosis, osteopenia, cancer, mood and anxiety disorders, infection) • Gastrointestinal outcomes (e.g., diarrhoea, cramping, bloating) • Adherence to gluten-free diet • Mucosal damage • Quality of life • Mortality • Cost-effectiveness		
Study designs	Randomised controlled trials (RCTs), cluster RCTs, non-randomised studies of interventions (NRSI), cost-effectiveness models	Comparative observational studies	

Question 4: What is the effectiveness of targeted versus universal screening for coeliac disease in symptomless adults?

Population	Symptomless adults
Intervention	Targeted screening of people with one or more specific risk marker that means that they are at more at risk of developing coeliac disease
Comparator	Universal screening of symptomless people
Outcomes	• Morbidity including outcomes related to nutritional deficiencies, such as symptomatic or severe anaemia [i.e., requiring treatment], osteoporosis, osteopenia, cancer, mood and anxiety disorders, infection, gastrointestinal outcomes (e.g., diarrhoea, cramping, bloating) • Adherence to gluten-free diet • Mucosal damage • Quality of life • Mortality • Cost-effectiveness
Study design	RCTs; NRSIs; economic models

Appendix 2 – Abstract reporting

Question 1: What is the prevalence of coeliac disease in high-risk groups?

Citation 1: Acharya et al (2020)[46]

Study type: Systematic review

Latest search date: Not reported in abstract

Number of included studies: 18 studies, 9 included in meta-analysis (N = not reported in abstract)

Objectives: To investigate the association between psoriasis and coeliac disease

Risk marker: Psoriasis

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Summary odds ratio quantifying association between coeliac disease and psoriasis: 2.16 (95% CI 1.74, 2.69; 9 studies)

Conclusions: The review identified a postive association between psoriasis and coeliac disease, and that patients with psoriasis who also report gastrointestinal symptoms may benefit from screening for coeliac disease.

Full text check: No

Citation 2: Al-Bluwi et al (2021)[38]

Study type: Systematic review

Latest search date: December 2019

Number of included studies: 36 studies (N = not reported in abstract), 4 studies reported comparative measures of association

Objectives: To quantify the weighted prevalence of coeliac disease among patients with Turner Syndrome and determine the weighted strength of association between turner syndrome and coeliac disease

Risk marker: Turner syndrome

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Two studies reported odds ratios (study 1: 18.1, 95% CI 1.82, 180; study 2: 4.34, 95% CI 1.48–12.75) and 2 studies reported rate ratios (study 3: 14, 95% CI 1.48, 12.75; study 4: 42.5, 95% CI: 12.4, 144.8) quantifying the association between Turner syndrome and

coeliac disease. The prevalence of coeliac disease in people with Turner syndrome was apprixmately 1 coeliac disease case in 22 people with Turner syndrome.

Conclusions: This review identified a positive association between Turner syndrome and coeliac disease, therefore patients with turner syndrome may benefit from screening for coeliac disease. In particular, the review noted that early detection of coeliac disease in turner syndrome may prevent adverse outcomes such as being underweight or developing osteoporosis.

Full text check: No

Citation 3: Castano et al (2019)[39]

Study type: Systematic review

Latest search date: June 2019

Number of included studies: 23 studies (N = not reported in abstract)

Objectives: To estimate the seroprevalence and biopsy confirmed prevalence of coeliac disease in people experiencing infertility

Risk marker: Infertility

Method of coeliac disease diagnosis: Seroprevalence and biopsy confirmed prevalence

Outcomes reported: Pooled prevalence of coeliac disease in people experiencing infertility was approximately 1.3% to 1.6%. Odds of having coeliac disease in people experiencing infertility compared to controls was 3-fold higher.

Conclusions: Further studies with increased sample sizes are necessary before giving specific recommendations for coeliac disease screening in women experiencing reproductive problems, but current data seems to support a higher risk of coeliac disease in this group.

Full text check: Yes: checked to ensure comparative data available, no data extracted from full text.

Citation 4: Clappison et al (2020)[36]

Study type: Systematic review

Latest search date: May 2019

Number of included studies: 37 studies (N = not reported in abstract)

Objectives: To provide a greater understanding of the existing evidence and theories surrounding psychiatricmanifestations of coeliac disease

Risk marker: Bipolar disorder, schizophrenia, ADHD, autism spectrum disorder

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Odds of marker in coeliac disease compared to healthy controls: autistic spectrum disorder (OR 1.53, 95% CI 1.24, 1.88,); ADHD (OR 1.39, 95% CI 1.18, 1.63); bipolar disorder (OR 2.35, 95% CI 2.29, 19.21) or schizophrenia (OR 0.46, 95% CI 0.02, 10.18)

Conclusions: Coeliac disease is associated with an increased risk of depression, anxiety, eating disorders, autism spectrum disorder and ADHD.

Full text check: Yes: checked to identify search data.

Citation 5: Elwenspoek et al (2021)[15]

Study type: Systematic review

Latest search date: April 2021

Number of included studies: 191 studies (N = not reported in abstract)

Objectives: To identify diagnostic indicators that may help identify patients at a higher risk of coeliac disease in whom further testing is warranted.

Risk marker: Family history of coeliac disease, multiple sclerosis, type 2 diabetes, arthritis, fracture, infertility, irritable bowel syndrome, systemic lupus erythematosus, inflammatory bowel disease, thyroid disease, psoriasis, chronic liver disease, osteoporosis, diabetes, anaemia, migraine, dermatitis herpetiformis

Method of coeliac disease diagnosis: Seroprevalence and biopsy confirmed prevalence

Outcomes reported: The review reported strong evidence that people with dermatitis herpetiformis, migraines, anaemia, type 1 diabetes, osteoporosis, or chronic liver disease are more likely than the general population to have coeliac disease. Psoriasis, epilepsy, inflammatory bowel disease, systemic lupus erythematosus, fractures, type 2 diabetes, and multiple sclerosis showed poor diagnostic ability. A sensitivity analysis revealed a 3-fold higher risk of coeliac disease in first-degree relatives of people with coeliac disease.

Conclusions: Targeting screening of people with specific risk factors such as dermatitis herpetiformis, anaemia, type 1 diabetes, a family history of the condition, osteoporosis, migraine, or chronic liver disease could improve case-finding for coeliac disease, therefore expediting appropriate treatment and reducing adverse consequences. Migraine and chronic liver disease are not yet included as a risk factor in all coeliac disease guidelines, but it may be appropriate for these to be added.

Full text check: No

Citation 6: Irvine et al (2017)[42]

Study type: Systematic review

Latest search date: May 2016

Number of included studies: 36 studies (N = 15,256)

Objectives: To evaluate whether individuals with irritable bowel syndrome should be screened for coeliac disease.

Risk marker: Irritable bowel syndrome

Method of coeliac disease diagnosis: Seroprevalence and biopsy-confirmed prevalence

Outcomes reported: Pooled odds ratios quantifying association between serological and biopsy-confirmed coeliac disease and irritable bowel syndrome: 3.21 (95% CI 1.55, 6.65) based on positive AGA; 2.75 (95% CI 1.35, 5.61) based on positive tTG or EMA; and 4.48 (95% CI 2.33, 8.60) based on positive biopsy.

Conclusions: Overall, the prevalence of positive coeliac serology and biopsy-proven coeliac disease was higher in people with symptoms of irritable bowel syndrome compared to healthy controls.

Full text check: No

Citation 7: Lasa et al (2014)[40]

Study type: Systematic review

Latest search date: December 2013

Number of included studies: 12 studies (N = not reported in abstract)

Objectives: To determine the relationship between celiac disease and infertility

Risk marker: Infertility

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Odds ratio quantifying association between experiencing infertility and undiagnosed celiac disease: 3.09, 95% CI 1.74, 5.49.

Conclusions: Undiagnosed celiac disease is a risk factor for infertility. Women seeking medical advice for infertility should be screened for celiac disease.

Full text check: Yes: Checked method of coeliac disease diagnosis, but it was not reported in full text

Citation 8: Nimri et al (2022)[44]

Study type: Systematic review

Latest search date: January 2022

Number of included studies: 26 studies (N = 22,802)

Objectives: To investigate the association between microscopic colitis and coeliac disease

Risk marker: Microscopic colitis

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Coeliac disease was significantly associated with microscopic colitis (OR: 8.276, 95% CI 5.888,11.632, p < 0.001). The event rate for microscopic colitis in coeliac disease patients was 6.2% (95% CI 4.1%, 9.2%, p < 0.001, while the event rate for coeliac disease in microscopic colitis patients was 6.1% (95% CI 3.9%, 9.5%, p < 0.001). Coeliac disease was prevalent in both types of microscopic colitis: 5.2% (95% CI 2.2%, 12.1%, p < 0.001) in collagenous colitis and 6.3% (95% CI 3.4%, 11.5%, p < 0.001) in lymphocytic colitis.

Conclusions: The review reported a positive association between microscopic colitis (both collagenous colitis and lymphocytic colitis) and coeliac disease.

Full text check: No

Citation 9: Pinto-Sanchez et al (2020)[43]

Study type: Systematic review

Latest search date: June 2019

Number of included studies: 65 studies, with 30 studies included in meta-analysis (13,679,013 participants were included in meta-anlysis)

Objectives: To assess investigate the association between coeliac disease and inflammatory bowel disease.

Risk marker: Inflammatory bowel disease

Method of coeliac disease diagnosis: Biopsy-confirmed prevalence

Outcomes reported: Risk ratio quantifying association between coeliac disease and inflammatory bowel disease: 3.96, 95% CI 2.23, 7.02; moderate certainty evidence.

Conclusions: People with inflammatory bowel disease were at increased risk of coeliac disease compared to other patient populations was found.

Full text check: Yes: Checked to identify the number of included participants and the method of coeliac disease diagnosis.

Citation 10: Quan et al (2021)[37]

Study type: Systematic review

Latest search date: Not reported in abstract

Number of included studies: 13 studies (N = not reported in abstract)

Objectives: To investigate the association between celiac disease and autism spectrum disorder

Risk marker: Autism spectrum disorder

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: The association between autism spectrum disorder and coeliac disease was unclear. Studies with smaller sample sizes did not detect an association, whereas larger higher quality studies showed a potential link.

Conclusions: The review concluded that additional research with larger sample sizes and precise definitions of coeliac disease and autism spectrum disorder is needed to further investigate this association, excluding people with autism spectrum disorder on a gluten-free diet.

Full text check: Yes: Checked to see if comparator was included, no data was extracted.

Citation 11: Singh et al (2022)[45]

Study type: Systematic review

Latest search date: May 2021

Number of included studies: 21 studies (N = 10,275)

Objectives: To assess the prevalence of coeliac disease in people with dyspepsia

Risk marker: Dyspepsia

Method of coeliac disease diagnosis: Seroprevalence and biopsy-confirmed prevalence

Outcomes reported: Odds ratio quantifying association between coeliac disease and dyspepsia, based on seroprevalence: 1.8 (95% CI 0.8, 4.0%; I^2 = 0%) and biopsy-confirmed prevalence 1.4 (95% CI 0.8, 2.4; I^2 = 0%). Pooled prevaence (1.5%).

Conclusions: There was no association between dyspepsia and having coeliac disease compared to the general population.

Full text check: No

Citation 12: Singh et al (2016)[41]

Study type: Systematic review

Latest search date: Not reported in abstract

Number of included studies: 5 studies (N = not reported in abstract)

Objectives: To investigate the association between people experiencing infertility and risk of coeliac disease.

Risk marker: Infertility

Method of coeliac disease diagnosis: Seroprevalence and biopsy-confirmed prevalence

Outcomes reported: Odds ratio quantifying association between coeliac disease and “all-cause infertility”: 3.5 (95% CI 1.3, 9) and in people with "unexplained infertility" 6.0 (95% CI 2.4, 14.6).

Conclusions: Women with "all-cause" infertility and "unexplained" infertility are at increased risk of having coeliac disease compared to the general population.

Full text check: No

Citation 13: Ungprasert et al (2017)[47]

Study type: Systematic review

Latest search date: Not reported in abstract

Number of included studies: 4 studies (N = 2,912 cases of psoriasis and 24,739 comparators)

Objectives: To summarize all available data on the possible association between psoriasis and celiac disease

Risk marker: Psoriasis

Method of coeliac disease diagnosis: Not reported in abstract

Outcomes reported: Odds ratio quantifying association between coeliac disease and psoriasis: 3.09 (95% CI 1.92, 4.97)

Conclusions: This meta-analysis reported an approximately 3-fold increased risk of coeliac disease among people with psoriasis.

Full text check: No

Question 2: What is the accuracy of screening tests for coeliac disease?

Citation 1: Chou et al (2017)[34]

Study type: Systematic review

Latest search date: June 2016

Number of included studies: One recent systematic review of 56 studies (N = not reported in abstract), 12 previous systematic reviews (N = 62 > 12,000) and 2 diagnostic test accuracy studies (N = not reported in abstract)

Objectives: To review the evidence on benefits and harms of screening for celiac disease in symptomless adults, adolescents, and children 3 years and older

Population: Not reported in abstract

Index test: IgA tTG or EMA

Reference standard: Not reported in abstract

Outcomes reported: Sensitivity; specificity

Results: Sensitivity and specificity of IgA tTG (> 90%), specificity of IgA EMA (raw data not reported in abstract, but abstract did state that there was high specificity), as well as IgG and IgA tTG sensitivity (IgG: 57%, IgA: 71%) and specificity (IgG: 93%, IgA: 98%) from 1 study of symptomless adults.

Conclusions: The review reported that further research is needed to understand the accuracy of screening tests in symptomless persons.

Full text check: Yes: Checked to identify specificity of tTG tests from the study of symptomless adults.

Citation 2: Diaz-Redondo et al (2015)[51]

Study type: Systematic review

Latest search date: December 2013

Number of included studies: 6 studies (N = 1,303)

Objectives: To investigate the diagnostic accuracy of HLA typing tests for celiac disease screening

Population: Not reported in abstract

Index test: HLA-DQ2 or 8

Reference standard: Not reported in abstract

Outcomes reported: Sensitivity; specificity; likelihood ratios

Results: Pooled sensitivity 98% (95% CI 97%, 99%); pooled specificity 45% (95% CI 41%, 48%), overall negative likelihood ratio (0.05, 95% CI: 0.03, 0.09). The review reported that specificity was heterogeneous by study and a subgroup analysis was done according to the type of population included (no further details reported in the abstract).

Conclusions: Due to the high sensitivity and low negative likelihood ratio, the review reported that HLA DQ2 or DQ8 typing would be an appropriate screening test for ruling out celiac disease in the general population with coeliac disease related symptoms, and more so in at risk populations (at risk populations not specified in abstract).

Full text check: No

Citation 3: Elwenspoek et al (2022)[16]

Study type: Systematic review

Latest search date: August 2020

Number of included studies: 4 studies (N = 12,087)

Objectives: To evaluate the accuracy of HLA DQ2 and DQ8 for the diagnosis of coeliac disease

Population: Not reported in abstract

Index test: HLA DQ2 or DQ8

Reference standard: Duodenal biopsy

Outcomes reported: Specificity; Sensitivity

Results: The summary sensitivity was 99% (95% CI 83%,100%) and specificity was 56% (95% CI 50%, 61%).

Conclusions: HLA may be a useful tests to rule out coeliac disease.

Full text check: Yes: Checked to identify the number of included studies, number of participants, and availability of 2x2 data. The scientific summary of the main report was also checked to obtain summary sensitivity and specificity.

Citation 4: Pjetraj et al (2024)[50]

Study type: Systematic review

Latest search date: March 2024

Number of included studies: 11 included in review, 7 included in meta-analysis (N = not reported in abstract)

Objectives: To conduct a systematic review and meta-analysis comparing CLIA with traditional enzyme-linked immunosorbent assay and fluorescence enzyme immunoassay).

Population: Not reported in abstract

Index test: tTG (IgA or IgG)

Reference standard: tTG based strategy; Duodenal biopsy

Outcomes reported: Specificity; Sensitivity

Results: Sensitivity and specificity of IgA tTG chemiluminescence immunoassay were 0.98 (95% CI 0.95, 0.99) and 0.97 (95% CI 0.94, 0.99), respectively. The sensitivity of IgA tTG did not significantly vary across the assay modalities examined:

- Chemiluminescence immunoassay compared to enzyme-linked immunosorbent assay (OR: 1.08, 95% CI 0.56, 2.11)
- Chemiluminescence immunoassay compared to fluorescence enzyme immunoassay (OR: 6.97 (95% CI 0.60, 81.03).

The specificity of IgA tTG assessed by fluorescence enzyme immunoassay was higher than for chemiluminescence immunoassay (OR: 0.17, 95% CI 0.05, 0.62).

Conclusions: According to the systematic review, normalisation of IgA tTG levels in coeliac disease patients following a gluten-free diet was delayed when using chemiluminescence immunoassay compared to enzyme-linked immunosorbent assay and fluorescence enzyme immunoassay methods. Conflicting findings were reported on the antibody threshold to use in order to avoid biopsy confirmation.

Full text check: No

Citation 5: Sheppard et al (2022)[16, 48]

Study type: Systematic review

Latest search date: August 2020

Number of included studies: 113 studies (N = 28,338)

Objectives: To assess the diagnostic accuracy of serological tests for coeliac disease in adults and children (results reported for adults only)

Population: Symptomatic

Index test: DGP (IgA or IgG), EMA (IgA or IgG), tTG (IgA or IgG)

Reference standard: Duodenal biopsy

Outcomes reported: Specificity; Sensitivity

Results: Summary sensitivity and specificity of IgA tTG were 90.7% (95% CI 87.3%, 93.2%) and 87.4% (95% CI 84.4%, 90.0%) in adults (5 studies). IgA EMA antibodies were 88% (95% CI 75.2%, 94.7%) and 99.6% (95% CI 92.3%, 100%) in adults (5 studies).

Conclusions: The high specificity of EMA in adults supports its use to rule in coeliac disease. This evidence underpins the current development of clinical guidelines for a serological diagnosis of coeliac disease. Studies in primary care are needed to evaluate serological testing strategies in this setting.

Full text check: No

Citation 6: Shiha et al (2024)[49]

Study type: Systematic review

Latest search date: October 2023

Number of included studies: 18 studies (N = 12,103)

Objectives: To evaluate the accuracy of the no-biopsy approach to confirm the diagnosis of celiac disease in adults

Population: Not reported in abstract

Index test: tTG (IgA or IgG)

Reference standard: Duodenal biopsy

Outcomes reported: PPV; Specificity; Sensitivity

Results: The pooled prevalence of biopsy-proven celiac disease in the included studies was 62% (95% CI 40%, 83%). The proportion of patients with IgA tTG ≥10× ULN was 32% (95% CI 24%, 40%). The summary sensitivity of IgA tTG ≥10× ULN was 51% (95% CI 42%, 60%), and the summary specificity was 100% (95% CI 98%, 100%). The area under the summary receiver operating characteristic curve was 0.83 (95% CI 0.77, 0.89).

Conclusions: Selected adult patients with IgA tTG ≥10× ULN and a moderate to high pretest probability of celiac disease could be diagnosed without undergoing invasive endoscopy and duodenal biopsy.

Full text check: Yes: Checked to identify if 2x2 data was reported, no data was extracted from full text

Citation 7: Singh et al (2019)[20]

Study type: Systematic review

Latest search date: July 2017

Number of included studies: Not reported in abstract

Objectives: To perform a systematic review and meta-analysis to estimate the overall diagnostic accuracy of point of care tests for diagnosing celiac disease.

Population: Not reported in abstracts

Index test: Point-of-care tests for tTG plus AGA, DGP, and tTG

Reference standard: Not reported in abstract

Outcomes reported: Likelihood ratios; Specificity; Sensitivity

Results: Pooled sensitivity and specificity for all point-of-care tests (based on tTG or DGP or tTG+Anti-gliadin antibodies) for diagnosing coeliac disease were 94.0% (95% CI 89.9, 96.5) and 94.4% (95% CI 90.9, 96.5), respectively. The pooled sensitivity for IgA-tTG-based point-of-care tests was 90.5% (95% CI 82.3, 95.1) and the pooled specificity was 94.8% (95% CI 92.5, 96.4). The pooled positive and negative likelihood ratios for point-of-care tests were 16.7 and 0.06, respectively.

Conclusions: The pooled sensitivity and specificity of point-of-care tests in diagnosing coeliac disease are high. Point-of-care tests may be used to screen for coeliac disease, especially in areas with limited access to laboratory-based testing. Further research assessing the diagnostic accuracy of individual point-of-care tests and comparing it with other available point-of-care testsis needed.

Full text check: No

Citation 8: Andersen et al (2025)[52]

Study type: One gate

Number of participants: 56,042 participants

Number of cases: 657 seropositive, 423 confirmed cases of coeliac disease

Objectives: To assess the accuracy of serological screening for coeliac disease in the adult general population.

Population: Screening

Index test: Dual assay to assess IgA and IgG tTG simultaneously.

Reference standard: Duodenal biopsy

Outcomes reported: PPV

Results: The PPV for a positive IgA tTG was 73.3% (95% CI 69.7%, 77.0%) for biopsy-confirmed coeliac disease, and 88.1% (95% CI 84.8%, 91.4%) at ≥10× the upper limit of normal. Among tTG IgA-negative individuals, the PPV for IgG tTG was 5.8% (95% CI 1.9, 12.9%), and 9.5% (95% CI 1.2%, 30.4%) at the 10× threshold (biopsy-confirmed coeliac disease).

Conclusions: The IgA tTG assay showed excellent abilities as a screening tool for coeliac disease in the adult general population. However, the diagnostic accuracy of IgG tTG was too poor for selectively identifying individuals with coeliac disease.

Full text check: No

Citation 9: Fuchs et al (2019)[53]

Study type: One gate

Number of participants: Three study cohorts: 421 adults with high-risk clinical coeliac disease suspicion (not relevant to this evidence map), 2,357 moderate-risk family members of coeliac disease patients, and 2,722 low-risk subjects from the general population

Number of cases: 274 cases (17 were family members of people with coeliac disease and 14 were low-risk subjects)

Objectives: To evaluate the accuracy of serology-based criteria in adults with variable pre-test probabilities for coeliac disease, including moderate-risk family members of coeliac disease patients low-risk subjects from the general population

Population: Screening population and risk group (family members of individuals with coeliac disease)

Index test: Triple criteria for diagnosis: tTG antibodies ≥10× ULN, positive EMA, and HLA DQ2 or DQ8

Reference standard: Duodenal biopsy

Outcomes reported: PPV

Results: Of the confirmed coeliac disease cases, 17 moderate-risk and 14 low-risk subjects were positive for tTG, EMA, and HLA DQ2 or DQ8. In participants positive on the triple criteria for diagnosis, the PPV was 100%. Altogether, 90 (33%) of all 274 newly diagnosed patients could have avoided biopsy, including 20% among moderate-risk, and 48% among low-risk patients.

Conclusions: Coeliac disease can reliably and safely be diagnosed without biopsy in adults fulfilling the "triple criteria" regardless of the pre-test probability. Revised criteria would enable the number of endoscopies to be reduced by one-third.

Full text check: No

Citation 10: Penny et al (2021)[55]

Study type: One gate

Number of participants: Cohort 1: 740 participants, cohort 2: 532 participants, cohort 3: 145 participants

Number of cases: Not reported in abstract.

Objectives: To determine the predictive capacity and diagnostic yield of a 10-fold increase in serum IgA antitissue transglutaminase antibody levels for detecting coeliac disease in adults

Population: Cohort 1: participants assessed in the specialist coeliac disease clinic at a UK centre; cohort 2: participants with low suspicion for coeliac disease referred for upper gastrointestinal endoscopy at a UK centre; cohort 3: participants with raised tTG titres from multiple international sites.

Index test: IgA tTG

Reference standard: Duodenal biopsy

Outcomes reported: Sensitivity; specificity; PPV; NPV

Results: In cohort 1, the sensitivity, specificity, PPV and NPV for IgA tTG levels of ≥10× ULN were 54.0%, 90.0%, 98.7% and 12.5%, respectively. In cohort 2, the sensitivity, specificity, PPV and NPV for IgA tTG levels of ≥10× ULN were 50.0%, 100.0%, 100.0% and 98.3%, respectively. In cohort 3, the sensitivity, specificity, PPV and NPV for IgA tTG levels of ≥10× ULN at were 30.0%, 83.0%, 95.2% and 9.5%, respectively.

Conclusions: IgA tTG titres of ≥10× ULN have a strong predictive value at identifying adults with intestinal changes diagnostic of coeliac disease. This study supports the use of a no-biopsy approach for the diagnosis of adult coeliac disease.

Full text check: No

Citation 11: Ylonen et al (2020)[56]

Study type: One gate

Number of participants: 836 participants (overall number with family risk of coeliac disease not reported in the abstract)

Number of cases: 85 cases of those with family risk (14%).

Objectives: To compare the performance of 4 TGA tests in the diagnosis of celiac disease in cohorts with diverse pre-test probabilities.

Population: Risk group: Family members

Index test: IgA tTG 10× the ULN and positive EMA

Reference standard: Duodenal biopsy: The diagnosis was set based on duodenal lesion or, in some cases, using special methods.

Outcomes reported: PPV

Results: The PPV for 10×ULN was 100% in each TGA test. Using the assays' own cut-offs (1× ULN) the PPVs ranged 84 to 100% (PPV for cases with family risk not reported separately in abstract from overall cohort)

Conclusions: Serology-based diagnosis of celiac disease was accurate in adults using different commercial kits and pre-test probabilities using 10xULN. The results also suggest that the ULN threshold for biopsy-omitting approach could be lower.

Full text check: No

Citation 12: Karhus et al (2016)[54]

Study type: One gate

Number of participants: 2,297 participants

Number of cases: 56 antibody positive, of which 8 had biopsy confirmed coeliac disease.

Objectives: To evaluate the diagnostic efficacy of serologic screening for celiac disease in an adult Danish population

Population: Screening

Index test: IgA tTG

Reference standard: Duodenal biopsy

Outcomes reported: PPV

Results: Of 8 biopsy confirmed participants, 7 were serologically positive at an IgA tTG antibodies threshold of 10 units/ml (PPV: 88%)

Conclusions: No conclusions relevant to diagnostic accuracy.

Full text check: No

Question 3: Does screen detection of coeliac disease and intervention provide better health outcomes than treatment of coeliac disease identified through symptoms, known high risk groups or opportunistic testing?

Citation 1: Cozzi et al (2022)[63]

Study type: Cross-sectional (comparative)

Number of participants: 59 participants

Number of cases: 59 cases (25 diagnosed with screening [mean age 28 years, 19 females] and 34 diagnosed for symptoms [mean age 25 years, 26 females])

Objectives: To investigate the compliance to the gluten-free diet in a cohort of adult celiac patients 20 years after the diagnosis, received in childhood through a mass screening.

Intervention: Screen detected coeliac disease

Comparator: Coeliac disease detected through symptoms

Follow up: 20 years

Outcomes reported: Adherence to gluten-free diet; autoimmune diseases

Results: Adherence to gluten-free diet after 20 years was optimal in 14 (56%), improvable in 5 (20%) and inadequate in 6 (24%) of those diagnosed with screening. Adherance to a gluten-free diet in those diagnosed for symptoms was optimal in 26 (81%), improvable in 3 (9%) and inadequate in 3 (9%). Development of autoimmune diseases was reported in 4 (16%) and 6 (18%) in those diagnosed with screening and for symptoms, respectively.

Conclusions: Twenty years after the diagnosis, nearly half of the patients diagnosed with mass screening, did not have an optimal adherence to the gluten-free diet and a remarkable proportion of them have developed another autoimmune disease.

Full text check: No

Citation 2: Kaur et al (2020)[66]

Study type: A prospective open label randomized controlled trial

Number of participants: 320 paricipants

Number of cases: 30 cases (including 15 on gluten-free diet, and 15 on gluten containing diet)

Objectives: To evaluate the effect of a gluten-free diet on the frequency of hypoglycaemia in patients with T1DM and subclinical (symptomless) coeliac disease, as well as a secondary objective to investigate the effect of a gluten-free diet on height, weight, glycosylated haemoglobin (HbA1c), insulin dose requirement, and bone mineral homeostasis.

Intervention: Gluten free diet

Comparator: Gluten containing diet

Follow up: 6 months

Outcomes reported: HbA1c; mean time spent in hypoglycaemia; number of hypoglycaemic episodes per month; morbidity

Results: The mean number of hypoglycaemic episodes per month recorded by self-monitoring of glucose was 2.3 episodes in the gluten-free diet group versus 3.4 episodes in the gluten containing diet group (p = 0.5). There was also a decrease in the mean number of hypoglycaemic episodes per month from baseline to follow-up at 6 months in the gluten-free diet group, from 3.5 episodes per month at baseline to 2.4 episodes at 6 months (p = 0.03). The mean time spent in hypoglycaemia, measured by continuous glucose monitoring devices, was 124.1 minutes in the gluten-free diet group compared to 356.9 minutes in the gluten containing diet group (p = 0.1). Mean haemoglobin A1c declined by 0.73% in the gluten-free diet group from baseline to 6 month follow-up, but increased by 0.99% in the gluten containing diet group over the same period.

Conclusions: The study reported a significant decrease in hypoglycaemic episodes from baseline to 6 month follow up in people with type 1 diabetes and symptomless coeliac disease following a gluten-free diet. The study reported a trend towards improved glycaemic control in the gluten-free diet group (HbA1c, mean number of hypoglycaemic episodes between groups and time spent in hypoglycaemia), but these differences were less clear statistically.

Full text check: No

Citation 3: Kivela et al (2018)[64]

Study type: Cross-sectional (comparative)

Number of participants: 236 participants

Number of cases: 236 cases

Objectives: To investigate health, quality of life and dietary adherence in adult coeliac patients diagnosed in childhood by screening.

Intervention: Symptomless or screen detected coeliac disease

Comparator: Coeliac disease detected through symptoms, high risk groups or opportunistic testing

Follow up: Patients completed the questionnaires a median of 18.5 years after childhood diagnosis.

Outcomes reported: General health or health concerns; mood and anxiety; adherence to gluten-free diet; quality of life

Results: Screen-detected patients (n = 48) had coeliac disease in the family and type 1 diabetes more often, and were less often smokers and members of coeliac societies compared

to clinically-detected patients, whereas the groups did not differ in current self-experienced health or health concerns, quality of life or dietary adherence (raw data not reported in abstract). Screen-detected, originally symptomless patients had more anxiety than those presenting with symptoms, whereas the subgroups were comparable in other current characteristics.

Conclusions: Comparable long-term outcomes between screen-detected and clinically-detected patients support risk-group screening for coeliac disease. However, symptomless patients may require special attention.

Full text check: No

Citation 4: Tovoli et al (2018)[65]

Study type: Cross-sectional (comparative)

Number of participants: 750 participants

Number of cases: 750 cases

Objectives: To investigate differences between screening detected and clinically diagnosed people with coeliac disease.

Intervention: Symptomless or screen detected coeliac disease

Comparator: Coeliac disease detected through symptoms, high risk groups or opportunistic testing

Follow up: Not reported in abstract

Outcomes reported: Gluten free diet-induced metabolic alterations; osteopenia; osteoporosis; non-responsive coeliac disease; adherence to gluten-free diet

Results: The groups shared a similar adherence to the gluten-free diet (91.2 versus 89.8%, $p = 0.857$). Moreover, the rates of non-responsive coeliac disease, gluten-free-diet-induced metabolic alterations, and persistence in controls were also similar. Instead, screening-detected patients had a significantly lower rate of osteopenia/osteoporosis at diagnosis (31.3 versus 46%, $p < 0.001$).

Conclusions: Screening strategies for CD in at-risk groups should be encouraged even in the adult population. Patients diagnosed through these strategies had no additional problems compared to those diagnosed for clinical suspicion and might benefit from a protective effect against metabolic bone disease.

Full text check: No

Question 4: What is the effectiveness of targeted versus universal screening for coeliac disease in symptomless adults?

Citation 1: Elwenspoek et al (2022)[16]

Study type: Economic model

Objectives: To evaluate the cost-effectiveness of CD testing of patients with pre-test probabilities of CD above certain thresholds using long-term economic models.

Targeted group: Different pre-test probabilities

Comparator group: Population screening

Outcomes reported: Cost-effectiveness

Results: The cost-effectiveness analysis found that, for serological testing alone, testing adult men and women who have a 1% pre-test probability (equivalent to population screening) had the highest net benefit, at £20,000 per quality-adjusted life-year . This resulted in incremental net benefits, relative to no screening, of £24,331 (95% credible interval (CrI) £5,080 to £56,493) for men and £24,382 (95% CrI £4829 to £59,154) for women. The serological tests (i.e. IgA EMA and IgA tTG) had similar cost-effectiveness and there was limited benefit to including both IgA EMA and IgA tTG tests. Strategies using both HLA and serological testing with pre-test probabilities of 1–20% had very similar net benefits to each other and to those of IgA tTG testing with 1% pre-test probability, and 95% CrIs were completely overlapping. The probability that any 1 test had the highest net benefit was <60% for adult men and 50% for adult women, suggesting uncertainty.

Conclusions: Based on the cost-effectiveness analysis, the most cost-effective strategy for adults, using serological testing alone, appears to be population-based screening (1% pre-test probability) using either the IgA tTG or IgA EMA test alone or both tests combined. However, there is substantial uncertainty in these results, and further research is needed prior to any implementation of screening. Given the wider availability of IgA tTG in UK laboratories, and the more objective nature of the test, IgA tTG the preferred serological test. Decisions to implement population-based screening should not be made based on this economic analysis alone: the proposed screening programme must meet UK National Screening Committee criteria. Although a CD screening programme meets some of these criteria, it does not yet meet all criteria. Additional required criteria are as follows: a consensus on an appropriate threshold for the screening test (i.e. IgA tTG), agreement on further diagnostic workup among those testing positive for IgA tTG and randomised trials showing the effectiveness of the screening programme.

Full text check: No: all data were extracted from the scientific summary

Appendix 3 - Additional relevant evidence

This section presents additional relevant evidence that, while not meeting the inclusion criteria, offers potentially valuable insights related to the review questions.

Review question 2 (accuracy of screening tests for coeliac disease)

Six potentially relevant conference abstracts were also identified for review question 2, but were excluded as conference abstracts did not meet the eligibility criteria for this evidence map.[57-62]. Of these, 1 looked at the diagnostic accuracy of tTG in populations with varying pre-test risk for coeliac disease,[57] 2 looked at the accuracy of no biopsy strategies for coeliac disease,[59, 62] and 3 looked at the diagnostic accuracy of tests for coeliac disease in high-risk groups (anaemia and multiple co-morbidities).[58, 60, 61]

Review question 3 (earlier detection and treatment of coeliac disease)

Although no systematic reviews were identified that directly fulfilled the inclusion criteria for this review question, we found 8 systematic reviews that we considered to provide potentially useful information on potential benefits of earlier detection and treatment of coeliac disease (Table 6).[67-73] Two systematic reviews compared outcomes among those with coeliac disease, including undiagnosed coeliac disease, and those without coeliac disease. One found an increased risk of mortality amongst those with coeliac disease, including undiagnosed coeliac disease (HR 1.09, 95% CI 0.95, 1.25).[74] Another found a greater risk of adverse birth outcomes amongst those with coeliac disease, including those with undiagnosed coeliac disease.[73, 74] Six systematic reviews looked at the impact of a gluten-free diet among people with coeliac disease on specific outcomes after starting a gluten-free diet.[67-72] Three of these measured the markers at the point of diagnosis and then again after a period of follow-up and 3 compared outcomes amongst those with coeliac disease not on a gluten-free diet to those with established coeliac disease on a gluten-free diet. Outcomes investigated included liver disease, mood and anxiety, bone mineral density, reflux disease, pancreatic insufficiency and thyroid disease. Most report beneficial effects of the gluten-free diet.

We also identified a further 2 primary studies that did not strictly fulfil our inclusion criteria but did provide relevant evidence on potential benefits of screen detection and treatment of coeliac disease (Table 7). A cross-sectional study involving a screening population reported that 71% of participants felt better on a gluten-free diet; this study did not meet full inclusion criteria due to the absence of a comparison group.[54] A case-control study found that individuals with undiagnosed coeliac disease identified through serological screening were more likely to develop complications such as osteoporosis, dermatitis herpetiformis, chronic fatigue, thyroiditis, and other autoimmune diseases compared to matched controls without coeliac disease.[75]

Table 6: Overview of systematic reviews that provided additional evidence on question 3 but did not meet inclusion criteria for this evidence map

Review	Search Date	Number of included studies (number of participants)	Outcomes	Results reported in abstract
People with coeliac disease, including those with undiagnosed coeliac disease, compared to those without coeliac disease				
Maimaris et al (2024)[74]	December 2022	25 studies (number of participants not reported in abstract)	Mortality	HR of mortality in individuals with coeliac disease compared to healthy controls: • All-cause mortality HR 1.2 (95% CI 1.1, 1.3) • Mortality due to malignancies HR 1.2 (95% CI 1.1, 1.4) • Mortality due to respiratory disease HR 1.4 (95 CI, 1.0, 1.9) • Mortality due to non-Hodgkin lymphoma HR 10.1 (95% CI 2.2, 46.9) Mortality significantly decreased in recent decades: • 1989 to 2004 (HR 1.6, 95% CI 1.2, 2.0) • 2005 to 2015 (HR 1.2, 95% CI 1.0, 1.4) • 2015 to 2022 (HR 1.2, 95% CI 1.0, 1.4) All-cause mortality was not increased in: • Dermatitis herpetiformis (HR 0.9. 95% CI 0.7, 1.0) • Undiagnosed coeliac disease (HR 1.1, 95% CI 1.0, 1.3) Mortality was increased in the UK (HR 1.2, 95% CI 1.0, 1.5) but not Scandinavia (HR 1.0, 95% CI 0.9, 1.1)
Saccone et al (2016)[73]	February 2015	10 studies (N = 4,844,555)	Birth outcomes	Compared with the control group, women with coeliac disease had a significantly higher risk of the development of: • Preterm birth (OR 1.4, 95% CI 1.1, 1.7) • Intrauterine growth restriction (OR 2.5, 95% CI 1.3, 4.7) • Stillbirth (OR 4.8, 95% CI 1.1, 21.8) • Low birth weight (OR 1.6, 95% CI 1.1, 2.5) • Small gestational age (OR 4.5, 95% CI 1.0, 20.1) No statistically significant difference was found in the incidence of preeclampsia (OR 2.5, 95% CI 0.9, 6.7). The risk of preterm birth was significantly higher both in the subgroup analysis of only women with diagnosed and treated celiac disease (OR 1.3, 95% CI 1.1, 1.5) and only women with undiagnosed and untreated celiac disease (OR 2.5, 95% CI 1.1, 5.9). Women with diagnosed and treated celiac disease had a significantly lower risk of the development of preterm birth, compared with undiagnosed and untreated celiac disease (OR 0.8, 95% CI 0.6, 1.0).
People with coeliac disease at baseline before starting gluten-free diet and at follow-up after following gluten-free diet.				

Review	Search Date	Number of included studies (number of participants)	Outcomes	Results reported in abstract
Jena et al (2023)[68]	March 2022	42 studies (N = 8,976)	Liver disease	Liver involvement was noted in 21.4% of coeliac disease patients (95% CI 17.0, 26.6). Coeliac hepatitis was reported in 49.2% (95% CI 30.1, 68.6) of coeliac disease patients. Compliance with gluten-free diet was noted in 90.3%. Response to gluten-free diet was noted in 86.4% (95 CI 80.0, 91.0).
Moawad et al (2024)[69]	Not reported in abstract	Not reported in abstract	Mood and anxiety	Coeliac disease patients are at a higher odds of developing anxiety (OR 2.3, 95% CI 1.2, 4.7) and depression (OR 3.4, 95% CI 1.4, 8.3). Results of both State-Trait Anxiety Inventory Y-1 and Y-2 improved after 1 year of gluten-free diet (MD 3.5, 95% CI 0.3, 6.7, and MD 3.5, 95% CI 1.4, 5.5), respectively.
Mosca et al (2022)[70]	July 2020	3 studies (N = 188)	Bone mineral density	Compared to healthy controls, our target population had lower bone mineral density. Moreover, a strict gluten-free diet may increase bone mineral density during a follow-up period of up to 5 years. Newly diagnosed coeliac disease patients aged 20-35 years are at risk of lower bone mineral density.
People with coeliac disease on gluten containing diet vs those on gluten-free diet				
Irani et al (2024)[67]	Not reported in abstract	31 studies (number of participants not reported in abstract)	Gastro-oesophageal reflux disease	Coeliac disease is strongly associated with gastro-oesophageal reflux disease but there was high heterogeneity (OR 10.2, 95% CI 6.5, 16.0). A gluten-free diet substantially improves symptoms of gastro-oesophageal reflux disease. (NOTE: Unclear if those on a gluten-free diet had coeliac disease).
Jiang et al (2023)[71]	Not reported in abstract	6 studies (N = 446)	Exocrine pancreatic insufficiency	Pooled prevalence of exocrine pancreatic insufficiency was 26% (95% CI 8, 44) in newly diagnosed coeliac disease patients and 8% (95% CI 2, 15) in patients treated with gluten-free diet. Patients with newly diagnosed coeliac disease are significantly more likely to have exocrine pancreatic insufficiency compared to those patients treated with gluten-free diet
Sun et al (2016)[72]	May 2016	13 studies (15,629 coeliac disease cases and 79,342 controls)	Thyroid disease	The prevalence of thyroid disease in patients with coeliac disease was significantly increased compared with that in the control groups (OR 3.1, 95% CI 2.7, 3.6). There was no significant difference in the OR between the gluten-treated and untreated groups (OR 1.1, 95% CI 0.6, 1.9).

Abbreviations: CI = confidence interval, HR = hazard ratio, MD = mean difference, OR = odds ratio

Table 7: Overview of primary studies that provided additional evidence on question 3 but did not meet inclusion criteria for this evidence map

Study	Study type	Study size	Follow up	Results reported in abstract
Hujoel et al (2018)[75]	Case control	400 undiagnosed coeliac patients identified through serological testing, and 400 unaffected age- and gender-matched controls were selected)	Not reported in abstract	• The odds of any indication for clinical testing were similar among undiagnosed coeliac disease and controls: OR 1.18 (95% CI 0.85, 1.63). • Most indications were not associated with serological status except for hypothyroidism, which is more likely in cases of undiagnosed coeliac disease, and dyspepsia and chronic diarrhoea, which were less likely. • Cases of undiagnosed coeliac disease were more likely to develop osteoporosis, dermatitis herpetiformis, chronic fatigue, thyroiditis, and autoimmune diseases, and have a family member diagnosed with coeliac disease
Karhus et al (2016)[54]	Cross-sectional (comparative)	2,297 adults in the Danish general population (of which 56 were antibody positive, and 8 had biopsy-confirmed coeliac disease)	5 years	• Most participants were satisfied with their participation in the screening programme • Of those diagnosed with coeliac disease, 71% reported feeling better on a gluten-free diet. • There were no differences in the prevalence of symptoms between patients with and without screening-detected coeliac disease.

Abbreviations: CI = confidence interval, OR = odds ratio

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