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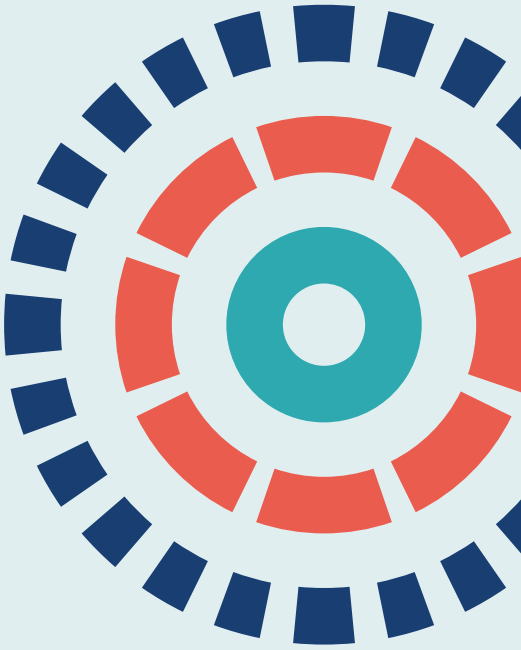

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Defining the optimum strategy for identifying adults and children with coeliac disease: systematic review and economic modelling

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This report

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Abstract

Defining the optimum strategy for identifying adults and children with coeliac disease: systematic review and economic modelling

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Background: Coeliac disease is an autoimmune disorder triggered by ingesting gluten. It affects approximately 1% of the UK population, but only one in three people is thought to have a diagnosis. Untreated coeliac disease may lead to malnutrition, anaemia, osteoporosis and lymphoma.

Objectives: The objectives were to define at-risk groups and determine the cost-effectiveness of active case-finding strategies in primary care.

Design: (1) Systematic review of the accuracy of potential diagnostic indicators for coeliac disease. (2) Routine data analysis to develop prediction models for identification of people who may benefit from testing for coeliac disease. (3) Systematic review of the accuracy of diagnostic tests for coeliac disease. (4) Systematic review of the accuracy of genetic tests for coeliac disease (literature search conducted in April 2021). (5) Online survey to identify diagnostic thresholds for testing, starting treatment and referral for biopsy. (6) Economic modelling to identify the cost-effectiveness of different active case-finding strategies, informed by the findings from previous objectives.

Data sources: For the first systematic review, the following databases were searched from 1997 to April 2021: MEDLINE® (National Library of Medicine, Bethesda, MD, USA), Embase® (Elsevier, Amsterdam, the Netherlands), Cochrane Library, Web of Science™ (Clarivate™, Philadelphia, PA, USA), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the National Institutes of Health Clinical Trials database. For the second systematic review, the following databases were searched from January 1990 to August 2020: MEDLINE, Embase, Cochrane Library, Web of Science,

Kleijnen Systematic Reviews (KSR) Evidence, WHO ICTRP and the National Institutes of Health Clinical Trials database. For prediction model development, Clinical Practice Research Datalink GOLD, Clinical Practice Research Datalink Aurum and a subcohort of the Avon Longitudinal Study of Parents and Children were used; for estimates for the economic models, Clinical Practice Research Datalink Aurum was used.

Review methods: For review 1, cohort and case–control studies reporting on a diagnostic indicator in a population with and a population without coeliac disease were eligible. For review 2, diagnostic cohort studies including patients presenting with coeliac disease symptoms who were tested with serological tests for coeliac disease and underwent a duodenal biopsy as reference standard were eligible. In both reviews, risk of bias was assessed using the quality assessment of diagnostic accuracy studies 2 tool. Bivariate random-effects meta-analyses were fitted, in which binomial likelihoods for the numbers of true positives and true negatives were assumed.

Results: People with dermatitis herpetiformis, a family history of coeliac disease, migraine, anaemia, type 1 diabetes, osteoporosis or chronic liver disease are 1.5–2 times more likely than the general population to have coeliac disease; individual gastrointestinal symptoms were not useful for identifying coeliac disease. For children, women and men, prediction models included 24, 24 and 21 indicators of coeliac disease, respectively. The models showed good discrimination between patients with and patients without coeliac disease, but performed less well when externally validated. Serological tests were found to have good diagnostic accuracy for coeliac disease. Immunoglobulin A tissue transglutaminase had the highest sensitivity and endomysial antibody the highest specificity. There was little improvement when tests were used in combination. Survey respondents ($n = 472$) wanted to be 66% certain of the diagnosis from a blood test before starting a gluten-free diet if symptomatic, and 90% certain if asymptomatic. Cost-effectiveness analyses found that, among adults, and using serological testing alone, immunoglobulin A tissue transglutaminase was most cost-effective at a 1% pre-test probability (equivalent to population screening). Strategies using immunoglobulin A endomysial antibody plus human leucocyte antigen or human leucocyte antigen plus immunoglobulin A tissue transglutaminase with any pre-test probability had similar cost-effectiveness results, which were also similar to the cost-effectiveness results of immunoglobulin A tissue transglutaminase at a 1% pre-test probability. The most practical alternative for implementation within the NHS is likely to be a combination of human leucocyte antigen and immunoglobulin A tissue transglutaminase testing among those with a pre-test probability above 1.5%. Among children, the most cost-effective strategy was a 10% pre-test probability with human leucocyte antigen plus immunoglobulin A tissue transglutaminase, but there was uncertainty around the most cost-effective pre-test probability. There was substantial uncertainty in economic model results, which means that there would be great value in conducting further research.

Limitations: The interpretation of meta-analyses was limited by the substantial heterogeneity between the included studies, and most included studies were judged to be at high risk of bias. The main limitations of the prediction models were that we were restricted to diagnostic indicators that were recorded by general practitioners and that, because coeliac disease is underdiagnosed, it is also under-reported in health-care data. The cost-effectiveness model is a simplification of coeliac disease and modelled an average cohort rather than individuals. Evidence was weak on the probability of routine coeliac disease diagnosis, the accuracy of serological and genetic tests and the utility of a gluten-free diet.

Conclusions: Population screening with immunoglobulin A tissue transglutaminase (1% pre-test probability) and of immunoglobulin A endomysial antibody followed by human leucocyte antigen testing or human leucocyte antigen testing followed by immunoglobulin A tissue transglutaminase with any pre-test probability appear to have similar cost-effectiveness results. As decisions to implement population screening cannot be made based on our economic analysis alone, and given the practical challenges of identifying patients with higher pre-test probabilities, we recommend that human leucocyte antigen combined with immunoglobulin A tissue transglutaminase testing should be considered for adults with at least a 1.5% pre-test probability of coeliac disease, equivalent to having at least one predictor. A more targeted strategy of 10% pre-test probability is recommended for children (e.g. children with anaemia).

Future work: Future work should consider whether or not population-based screening for coeliac disease could meet the UK National Screening Committee criteria and whether or not it necessitates a long-term randomised controlled trial of screening strategies. Large prospective cohort studies in which all participants receive accurate tests for coeliac disease are needed.

Study registration: This study is registered as PROSPERO CRD42019115506 and CRD42020170766.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/ZUCE8371).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
ARC	Applied Research Collaboration
AUROC	area under the receiver operating characteristic
BCEA	Bayesian cost-effectiveness analysis
CD	coeliac disease
CD-QOL	Coeliac Disease Quality of Life Measure 1.0
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CrI	credible interval
DGP	deamidated gliadin peptide
DTA	diagnostic test accuracy
EMA	endomysial antibody
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESsCD	European Society for the Study of Coeliac Disease
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
GA	gliadin antibody
GI	gastrointestinal
GP	general practitioner
HES	Hospital Episode Statistics
HLA	human leucocyte antigen
IBS	irritable bowel syndrome
ICER	incremental cost-effectiveness ratio
ICPC-2	*International Classification of Primary Care*, 2nd edition
ICTRP	International Clinical Trials Registry Platform
ID	identification
IDA	iron-deficiency anaemia
IgA	immunoglobulin A
IgG	immunoglobulin G
IMD	Index of Multiple Deprivation
IQR	interquartile range
KSR	Kleijnen Systematic Reviews
LASSO	least absolute shrinkage and selection operator
MLMC	multilevel Monte Carlo
NHL	non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health and Care Research
OGD	oesophagogastroduodenoscopy
PPV	positive predictive value
PRISMA-DTA	Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies
QALY	quality-adjusted life-year
QUADAS-2	quality assessment of diagnostic accuracy studies 2
ROC	receiver operating characteristic

SD	standard deviation	tTG	tissue transglutaminase
SE	standard error	UTS	up to standard
SROC	summary receiver operating characteristic	WHO	World Health Organization

Plain English summary

What is the problem?

Around 1 in 100 people in the UK has coeliac disease. It develops when the immune system attacks the lining of the gut after eating gluten. It is thought that only one in three people with coeliac disease is currently diagnosed. Without treatment, people with coeliac disease are at an increased risk of anaemia, osteoporosis and cancer. Treatment is a lifelong gluten-free diet.

Diagnosing coeliac disease is difficult. Some people have minimal or non-specific symptoms, such as pain, indigestion or bloating, so knowing who to test is tricky.

What did we do?

We wanted to establish who should be tested for coeliac disease, what tests should be used and whether or not invasive testing (a gut biopsy) is necessary for everyone. We looked at existing studies and data from general practices, and conducted an online survey, and brought everything together in an economic (cost) analysis.

What did we find?

Using individual symptoms is not helpful to identify people who may have coeliac disease. People with coeliac disease are more likely to have a combination of symptoms. People with anaemia, type 1 diabetes, osteoporosis, thyroid disorders, immunoglobulin A deficiency, Down syndrome, Turner syndrome or a family history of coeliac disease are more likely to have coeliac disease and should be offered tests.

Common blood tests for coeliac disease are very accurate, particularly when used in combination with genetic testing. Blood tests alone can be used for diagnosis for some people. Others will need a biopsy to confirm the diagnosis. Whether or not this is needed depends on their risk of coeliac disease: whether or not they have symptoms and whether or not they have a condition that puts them at higher risk. Shared decision-making is important for individuals considering an invasive test, depending on how certain they want to be about their diagnosis before starting a gluten-free diet.

Scientific summary

Background

Coeliac disease (CD) is an autoimmune disorder, triggered by the protein gluten, which affects an estimated 1% of the UK population. Some people with CD may have minimal symptoms; and others present with non-specific symptoms, making diagnosis difficult: only one in three is thought to be diagnosed. Treatment for CD is lifetime adherence to a gluten-free diet. Untreated CD may lead to persistent symptoms, anaemia, osteoporosis and, occasionally, lymphoma. Guidelines recommend that adults and children 'at high risk' of CD should be offered testing. However, it is not clear which groups are at sufficiently high risk to justify testing, which symptoms should prompt testing, which tests should be offered or if confirmatory biopsy is necessary.

Objectives

The overall aim of this project was to define at-risk groups and determine the cost-effectiveness of active case-finding in primary care.

We defined the following objectives to address this overall aim:

- systematic review of the accuracy of potential diagnostic indicators for CD
- routine data analysis to develop a prediction model to identify people who should be tested for CD
- systematic review of the accuracy of diagnostic tests for CD
- systematic review of the accuracy of genetic tests for CD
- online survey to identify diagnostic thresholds for testing, starting treatment and referral for biopsy
- economic modelling to identify the cost-effectiveness of different active case-finding strategies, informed by the findings of the previous objectives.

Methods

Accuracy of diagnostic indicators

For the first review, six databases [MEDLINE® (National Library of Medicine, Bethesda, MD, USA), Embase® (Elsevier, Amsterdam, the Netherlands), Cochrane Library, Web of Science™ (Clarivate™, Philadelphia, PA, USA), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the National Institutes of Health Clinical Trials database] were searched from January 1990 to April 2021. Studies investigating diagnostic indicators, such as symptoms or risk conditions, among people with and people without CD were eligible for inclusion. International guidance for systematic review methods was followed and the reviews were registered at PROSPERO. Risk-of-bias assessments were performed using the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool. Bivariate random-effects meta-analyses were used to pool sensitivity and specificity across studies.

Prediction model development

For the prediction models, we used three data sets: two primary care databases (Clinical Practice Research Datalink Gold and Aurum) containing routinely collected primary care data and a subcohort of the Avon Longitudinal Study of Parents and Children. We fitted logistic regression models with CD as the outcome and multiple diagnostic indicators as predictors. From the results, we produced estimates of discrimination and calibration of the models, the accuracy of predictions at different thresholds and the percentage of people with CD who were missed at these thresholds.

Accuracy of serological tests

For the second systematic review on the accuracy of tests for CD, seven electronic databases [MEDLINE, Embase, Cochrane Library, Web of Science, Kleijnen Systematic Reviews (KSR) Evidence, the WHO ICTRP and the National Institutes of Health Clinical Trials database] were searched from January 1990 to August 2020. We included diagnostic cohort studies that evaluated serological tests for CD [i.e. immunoglobulin A (IgA) tissue transglutaminase (tTG), immunoglobulin G (IgG) tTG, IgA endomysial antibody (EMA), IgG EMA, IgA deamidated gliadin peptide (DGP), IgG DGP and IgA actin antibody] among people presenting with symptoms suggestive of CD.

Accuracy of genetic tests

The review of the accuracy of genetic tests for CD was based on the same search used for the first review of diagnostic indicators and included studies that provided accuracy on the combination of human leucocyte antigen (*HLA*)-*DQ2*/*DQ8* testing. All reviews followed the same internationally recognised methods for systematic reviews.

Online survey

We developed an online survey in collaboration with patient representatives to identify how confident people want to be in their diagnosis before starting a gluten-free diet or accepting a biopsy. The survey was open for 2.5 months (January–March 2021) and was disseminated using social media.

Economic modelling

The cost-effectiveness of CD testing of patients with pre-test probabilities of CD above certain thresholds was evaluated with long-term economic models. We used a decision tree and discrete-time cohort Markov model to compare the cost-effectiveness of case-finding strategies at different levels of pre-test probability separately for men, women and children.

Results

Accuracy of diagnostic indicators

The review of diagnostic indicators included 183 studies reporting on 25 indicators, which comprised seven symptoms, 17 risk conditions and family history. There was large variation in diagnostic accuracy estimates between studies, and most studies were at high risk of bias. None of the identified diagnostic indicators alone had good sensitivity for detecting CD; however, some showed promise in helping to identify patients who should be offered serological testing. The estimated positive predictive values for migraine, family history of CD, anaemia, type 1 diabetes, osteoporosis and chronic liver disease were all > 2%, with 95% confidence intervals (CIs) lying entirely above the population prevalence of 1%. Individual gastrointestinal symptoms showed poor diagnostic ability. People with a first-degree relative with CD were three times more likely to have CD than the general population.

Prediction model development

We developed prediction models for children, women and men that comprised 24, 24 and 21 predictors, respectively. For children, having type 1 diabetes, Turner syndrome, IgA deficiency or a first-degree relative with CD were estimated to be the strongest predictors (i.e. had the highest estimated coefficients). For women and men, the strongest predictors were having a first-degree relative with CD, or having anaemia. In the development data set, the model showed good discrimination between patients with and patients without CD, as demonstrated by high *c*-statistics of 0.84 (95% CI 0.83 to 0.84) for children, 0.77 (95% CI 0.77 to 0.78) for women and 0.81 (95% CI 0.81 to 0.82) for men. The model discriminated less well between patients with and patients without CD in the external validation data set, for which the *c*-statistics reduced to 0.60 for children, 0.55 for women and 0.62 for men. However, the predictor first-degree relative was not recorded in the validation data set, which was one of the most important predictors, leading to an underestimation of model performance in this data set. The models were poorly calibrated and tended to overestimate the

risk of having CD in all three groups in the development data set and validation data set. The models suggest that individuals with any of the selected predictors have an increased risk of CD of > 50%, and thus warrant testing for CD.

Accuracy of serological tests

The review of test accuracy included 113 studies ($n = 28,338$), all in secondary care populations. A subset of studies was included in meta-analyses because of variations in diagnostic thresholds. The majority of included studies were at high risk of bias. The summary sensitivity and specificity of the IgA tTG test were 91% (95% CI 87% to 93%) and 87% (95% CI 84% to 90%), respectively, for adults (five studies) and 98% (95% CI 91% to 99%) and 70% (95% CI 39% to 90%), respectively, for children (six studies). The summary sensitivity and specificity of the IgA EMA test were 88% (95% CI 75% to 95%) and 99.6% (95% CI 92% to 100%), respectively, for adults (five studies) and 95% (95% CI 89% to 97%) and 94% (95% CI 85% to 98%), respectively, for children (five studies). To select estimates to inform the economic model, we restricted our analyses to studies that had evaluated the two main serological tests of interest (IgA tTG and IgA EMA, alone and in combination) at the same threshold. This was to ensure that estimates used in the economic model were directly comparable. None of the studies that evaluated both tests alone and in combination reported accuracy estimates for the same thresholds. We therefore selected the studies that were judged to have the lowest risk of bias and that had the largest sample sizes. For both adults and children, the IgA tTG test had the highest sensitivity, although estimates for children were very similar, and the IgA EMA test had the highest specificity. There was little improvement in either sensitivity or specificity when the tests were used in combination.

Accuracy of genetic tests

Four studies ($n = 12,087$) evaluated the accuracy of *HLA-DQ2* and/or *-DQ8* genetic variants for diagnosing CD. Three studies were deemed to be at low risk of bias, and one was deemed to be at high risk of bias, as serology alone was used to confirm CD status. The summary sensitivity was 99% (95% CI 83% to 100%) and specificity was 56% (95% CI 50% to 61%), suggesting that it would be a useful test to rule out CD.

Online survey

The survey was completed by 472 people. Of these, 244 (52%) had CD, with the disease confirmed by a blood test and/or biopsy. Among those who completed the demographic questions, the vast majority were white ($n = 264$, 95%) and female ($n = 239$, 86%); most respondents went to university or college ($n = 159$, 58%) and lived in the south-west of England ($n = 98$, 36%). Survey respondents wanted to be 66% [median interquartile range (IQR) 33–90%] certain of the diagnosis before starting a gluten-free diet when they were asked to imagine that they had CD symptoms. Without symptoms, respondents wanted to be more certain, around 90% (median IQR 66–99%), before committing to a gluten-free diet. However, a higher proportion of respondents opted to wait for a confirmation biopsy, if given the option, instead of starting a gluten-free diet immediately, even if a hypothetical blood test gave 75–90% certainty.

Economic modelling

The cost-effectiveness analysis found that, for serological testing alone, testing adult men and women who have a 1% pre-test probability (i.e. testing all adults with a 1% pre-test probability of CD, which is equivalent to population screening) had the highest net benefit, at £20,000 per quality-adjusted life-year (QALY). This resulted in incremental net benefits, relative to no screening, of £24,331 [95% credible interval (CrI) £5080 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 one test had the highest net benefit was < 60% for adult men and 50% for adult women, suggesting uncertainty.

Among children, testing all those with a pre-test probability of ≥ 10% with HLA plus IgA tTG had the greatest net benefit at £20,000 per QALY, with an incremental net benefit of £13,090 (95% CrI £3929 to £36,260), relative to no screening; it also had the highest probability (≈ 80%) of being cost-effective at > £10,000 per QALY. Again, there was limited difference in cost-effectiveness between pre-test probabilities, so long as either IgA EMA plus HLA or HLA plus IgA tTG was used as the testing combination.

There was substantial uncertainty in these results, and a value-of-information analysis indicated that they were sensitive to the probability of diagnosis of CD during routine care and the accuracy of HLA and serological tests. The total population expected value of perfect information was £25.7M for men, £79.0M for women and £18.4M for children, indicating potential value of further research, particularly for women.

Conclusions

Implications for practice

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 is probably 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.

Given that population screening is not considered appropriate, we recommend a strategy for adults that combines HLA testing with IgA tTG among those with at least a 1.5% pre-test probability of having CD. These strategies had nearly identical cost-effectiveness to that of the IgA tTG test with 1% pre-test probability, based on our cost-effectiveness analysis. They also had similar cost-effectiveness to more targeted strategies with pre-test probabilities of 5–20%, and people with lower pre-test probabilities are easier to identify, based on our review of diagnostic indicators and prediction models. For children, the most cost-effective testing strategy is to test those with a 10% pre-test probability of CD (more cost-effective than population screening). Therefore, indicators that should prompt testing are those that increase the risk of CD to at least 1.5% among adults (equivalent to at least one of the identified predictors) and to 10% among children, that is children with certain high-risk predictors (e.g. anaemia) or a combination of lower-risk predictors (e.g. failure to thrive and gastrointestinal symptoms). These are diagnostic indicators identified by our review of diagnostic indicators and through the prediction model. The most predictive indicator in all populations was having a first-degree relative with CD. Other indicators identified by our review, but not currently recommended in existing guidelines, that should prompt testing include migraine and chronic liver disease.

The cost-effectiveness analysis found that HLA testing prior to IgA tTG testing was the most cost-effective ordering of these tests. However, in practice such a strategy may have unintended costs and consequences not captured by the economic model. A strategy whereby serological testing is performed first may therefore be preferable, although this would be likely to lead to a greater number of false-negative and false-positive results overall.

All strategies assumed that biopsy would be recommended if the post-test probability following positive test results remained < 90%. Whether or not this is the case will depend on the pre-test probability of disease, and so it may be difficult to implement such a strategy in practice. The variation among individuals in their preferred diagnostic certainty and attitudes towards having a biopsy or following a gluten-free diet suggests that shared decision-making in which patient preferences are taken into account is important in determining the 'optimum' diagnostic pathway.

Suggested research priorities

Given that one of the most cost-effective strategies based on our cost-effectiveness analysis was population-based screening, future work should consider whether or not population-based screening for CD could meet the UK National Screening Committee criteria.

A value-of-information analysis suggested that future research should focus on the probability of CD diagnosis during routine care and the accuracy of serological and HLA testing.

There is a need for large prospective cohort studies in which all participants receive accurate tests for CD, to provide a more accurate estimate of the diagnostic ability of indicators and to develop a more robust clinical prediction model.

Study registration

This study is registered as PROSPERO CRD42019115506 and CRD42020170766.

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Chapter 1 Objectives

The overall aim of this project was to define at-risk groups and determine the cost-effectiveness of active case-finding strategies in primary care.

We defined the following six objectives to address this overall aim:

1. systematic review of the accuracy of potential diagnostic indicators for coeliac disease (CD) (see *Chapter 3*)
2. routine data analysis to develop a prediction model to identify people who should be tested for CD (see *Chapter 4*)
3. systematic review of the accuracy of diagnostic tests for CD (see *Chapter 5*)
4. systematic review of the accuracy of genetic tests for CD (see *Chapter 6*)
5. online survey to identify diagnostic thresholds for testing, starting treatment and referral for biopsy (see *Chapter 7*)
6. economic modelling to identify the cost-effectiveness of different active case-finding strategies, informed by the findings of previous objectives (see *Chapter 8*).

Chapter 2 Background

Overview of coeliac disease

Coeliac disease is an autoimmune disorder triggered by the protein gluten, which is found in wheat, rye and barley.[1] Some people with CD may be asymptomatic; others present with non-specific symptoms, including gastrointestinal (GI) symptoms (e.g. diarrhoea, bloating, gassiness, constipation, vomiting or abdominal pain), fatigue and unexplained weight loss. CD is estimated to affect around 1% of people in the UK;[2] however, only 30% of those with the condition are thought to be diagnosed.[3]

The only currently available treatment for CD is lifetime adherence to a gluten-free diet, which can be difficult and restrictive, significantly affecting a person's quality of life, meaning that it is important to be confident that a CD diagnosis is correct. If CD is not diagnosed promptly and the condition remains untreated, damage may be sustained to the surface of the small intestine and difficulty absorbing nutrients may lead to malnutrition, anaemia and/or osteoporosis.[4] In the long term, untreated CD may lead to a higher risk of serious complications, such as lymphoma, osteoporosis and small-bowel cancer.[5,6]

New treatments are in the development pathway, but most are still in pre-clinical phases. These aim to allow people with CD to be able to eat gluten, or to prevent inadvertent gluten contamination, without becoming symptomatic or damaging the intestinal lining.[7]

Diagnostic pathway

The diagnostic pathway for CD broadly involves the following steps:

1. identification of those at risk of CD who should be tested
2. serological testing to identify potential CD
3. biopsy confirmation of the diagnosis.

However, there is lack of consensus across different guidelines on the exact diagnostic pathway: who should be tested, what tests they should have and whether or not biopsy confirmation is required.

Identifying people at risk who should be tested

Within the current diagnostic pathway for CD, adults and children 'at high risk' of CD should be offered testing. However, there is a lack of consensus regarding who should be tested and whether or not certain groups of people are at sufficiently high risk to justify routine testing, or whether or not population-based screening may be appropriate. A 2021 cost-effectiveness analysis[8] estimated that the cost of mass screening for CD at age 12 years was €40,105 per quality-adjusted life-year (QALY) gained; this is cost-effective at the commonly used threshold of €50,000 per QALY gained. If mass screening is not considered appropriate, it is not clear (1) what symptoms or conditions are suggestive of CD and (2) which of these should prompt testing, with recommendations varying across guidelines.

The National Institute for Health and Care Excellence (NICE) guidelines, published in 2015,[9] recommend that people with any of the following symptoms or conditions be offered serological testing for CD:

- persistent unexplained abdominal or GI symptoms
- faltering growth (children only)
- prolonged fatigue
- unexpected weight loss

- severe or persistent mouth ulcers
- unexplained iron, vitamin B_{12} or folate deficiency
- type 1 diabetes
- autoimmune thyroid disease
- irritable bowel syndrome (IBS) (adults only).

Furthermore, the guidelines recommend that first-degree relatives of people with CD be offered serological testing for CD.

The guidelines also suggest that serological testing for CD could be considered for people with any of the following symptoms or conditions:

- metabolic bone disorder (reduced bone mineral density or osteomalacia)
- unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
- unexplained subfertility or recurrent miscarriage
- persistently raised liver enzymes with unknown cause
- dental enamel defects
- Down syndrome
- Turner syndrome.

Other guidelines vary in recommendations on who should be tested for CD. For example, the 2020 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines[10] for the diagnosis of paediatric CD suggest that children and adolescents with the following symptoms or conditions should be tested:

- chronic or intermittent diarrhoea, constipation/abdominal pain, distended abdomen or recurrent nausea and/or vomiting
- failure to thrive
- delayed puberty, amenorrhoea
- irritability
- arthritis/arthralgia
- recurrent aphthous stomatitis
- dermatitis herpetiformis-type rash
- Williams–Beuren syndrome
- immunoglobulin A (IgA) deficiency
- liver disease.

The European Society for the Study of Coeliac Disease (ESsCD) 2019 guidelines[11] recommend testing in the following additional groups:

- microscopic colitis
- early menopause
- acute or chronic pancreatitis
- epilepsy
- headaches, including migraines
- mood disorders
- attention deficit disorder/cognitive impairment
- hyposplenism or functional asplenia, psoriasis or other skin lesions, pulmonary haemosiderosis, and IgA nephropathy.

Serological testing

There are a number of serological tests available for CD. These are summarised in *Table 1*. For all currently available serological tests, patients must continue to eat gluten daily for the 6 weeks prior to testing. Recommendations for serological testing for CD also vary across guidelines. Most guidelines recommend that people identified as potentially being at risk of having CD are first tested for IgA and IgA tissue transglutaminase (tTG).[9,10] Some guidelines also recommend IgA endomysial antibody (EMA) testing following tTG testing: NICE guidelines recommend that those with a weak positive IgA tTG should also be tested with IgA EMA.[9] In practice, EMA testing is often conducted following a positive tTG test to confirm the diagnosis. Testing for IgA deficiency is recommended, as the IgA-based serological tests will produce a reliable result only for those who are not IgA deficient. IgA deficiency affects around 0.5% of the general population, but is more common among those with CD, affecting around 2–3%. If IgA deficiency is detected, then an immunoglobulin G (IgG)-based test alternative is required; NICE[9] and ESPGHAN[10] guidelines recommend IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG. Gliadin antibodies (GAs) and reculin antibodies, which were previously recommended for serological testing for CD, are now no longer recommended, as the more recently developed assays are considered to have better accuracy.[11]

Previous systematic reviews of the accuracy of serological testing for diagnosing CD suggest that the tests are highly sensitive and specific among both adults and children.[12–15] However, these systematic reviews are out of date, and most have methodological limitations, including issues with the search strategy, how study quality was assessed and how results were synthesised.

Genetic testing

Coeliac disease has a strong genetic basis. Nearly all people with CD have variants of the human leucocyte antigen (HLA)-DQ alpha 1 (*HLA-DQA1*) and HLA-DQ beta 1 (*HLA-DQB1*) chains that encode the DQ2 and DQ8 heterodimer proteins.[16] The majority of people with CD (95%) carry the HLA-DQ2.5 heterodimer. The remaining people (5–10%) carry either the HLA-DQ8 or the HLA-DQ2.2 heterodimers. It is estimated that < 1% of those with CD do not have one of these genetic markers. However, around 50% of the general population also carry these markers, so presence of the marker does not equate to presence of CD.[17]

The role of genetic testing in diagnosing CD is unclear. It has the potential to be used as a 'rule-out' test, as absence of either the *HLA-DQ2* or the *HLA-DQ8* genetic marker suggests that it is extremely unlikely that the person tested has CD. However, the presence of these markers does not imply presence of CD, and so it is less useful as a rule-in test. The cost of genetic testing is greater than the cost of serology and, therefore, guidelines do not currently recommend *HLA-DQ2/-DQ8* testing as an initial screening test for CD diagnosis.

TABLE 1 Serological tests for CD

Serological test	Antibody type	Date available	Test type	Guidelines	UK cost (£)
tTG	IgA or IgG	1997	ELISA	NICE;[9] ESPGHAN[10]	10.77 (SE 2.15)
EMA	IgA or IgG	≈ 1990	IFA	NICE;[9] ESPGHAN[10]	14.92 (SE 1.87)
DGP	IgA or IgG	1999	ELISA	NICE;[9] ESPGHAN[10]	NA
Actin antibodies	IgA	≈ 2000	ELISA	Not recommended	NA
Reculin antibodies	IgA or IgG	1977	IFA (rat kidney)	Not recommended	NA
GAs	IgA or IgG	Early 1980s	Quantitative EIA	Not recommended	NA

DGP, deamidated gliadin peptide; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; EMA, endomysial antibody; GA, gliadin antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; NA, not available; SE, standard error; tTG, tissue transglutaminase.

The NICE guidelines[9] recommend against using *HLA-DQ2/-DQ8* testing in the initial diagnosis of CD in non-specialist settings, but suggest that testing may be considered in certain situations, such as for children who are not having a biopsy or for people who have already stopped eating gluten and do not want to reintroduce it into their diet.

Biopsy confirmation

Biopsy is invasive, expensive, potentially distressing and burdensome, with risks of complications, particularly for children, who require general anaesthesia to undergo the procedure. NICE guidelines recommend biopsy to confirm a diagnosis of CD for all adults with positive serological test results, regardless of how strongly indicative their results are of CD. The guidance for children is less clear: NICE guidelines recommend that children with a positive serological test are referred to paediatric gastroenterology services for further investigation for CD. They do not specify that this should be biopsy confirmation. As with serological tests, patients must eat gluten daily in the 6 weeks prior to biopsy for the result to be reliable.

In its 2012 guidelines,[18] ESPGHAN advised that children with IgA tTG $\geq$ 10 times the upper limit of normal for the assay who also test positive for IgA EMA and have a HLA genotype suggestive of CD do not need to undergo biopsy to confirm their CD diagnosis.[18] During the COVID-19 pandemic, the British Society of Gastroenterology published interim guidance including a COVID-19-specific non-biopsy protocol for adults with suspected CD.[19] This guidance allows a non-biopsy diagnosis to be made if the patient has a tTG level $\geq$ 10 times the upper limit of normal (the same as the non-biopsy protocol for children), is $<$ 55 years of age, has a positive EMA test result and does not have any 'alarm' symptoms, although it is not clear what these are.[19]

Some guidelines recommend biopsy even if serological tests for CD are negative in certain patient groups. For example, the ESsCD 2019 guidelines[11] recommend biopsy for those with chronic diarrhoea, particularly with features of malabsorption, such as weight loss; iron-deficiency anaemia (IDA) without cause; GI symptoms with a family history of CD; GI symptoms and an autoimmune disease or IgA deficiency; or biopsy-proven dermatitis herpetiformis. They also recommend biopsy for 'failure to thrive in children'.[11] NICE guidelines recommend referral of people with 'negative serological test results to a gastrointestinal specialist for further assessment if coeliac disease is still clinically suspected'[9] (© NICE 2015 *Coeliac Disease: Recognition, Assessment and Management*; available from www.nice.org.uk/guidance/ng20 All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication).

Chapter 3 Accuracy of diagnostic indicators for coeliac disease

We conducted a systematic review to assess the accuracy of various symptoms and risk factors in 'diagnosing' CD, considering the potential of these as initial screening tools prior to serological testing. In this chapter, we will refer to these symptoms and risk factors as 'diagnostic indicators'. We defined diagnostic indicators as signs, symptoms and risk factors that may help clinicians identify patients for whom further testing for CD is warranted. We did not consider factors that are difficult to determine at an initial consultation, such as perinatal risk factors or age at gluten introduction, or experimental factors that are not measured in clinical practice [i.e. tests for susceptibility genes; these are currently not widely available to clinicians and therefore are not (yet) useful in aiding diagnosis].

The review was registered with the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42020170766. We published the protocol for the review, which predefined the objectives and methods for this review.[21] This review followed the recommendations from the Centre for Reviews and Dissemination[22] and the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0*,[23] and is reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement.[24]

Systematic review methods

Eligibility criteria

Studies were evaluated as diagnostic test accuracy (DTA) studies; the diagnostic indicator was considered to be the index test and CD serological tests and/or biopsy were considered the reference standard.

We included studies that met the following criteria:

- Study design – diagnostic cohort/cross-sectional studies (also known as 'one-gate design')[25] or diagnostic case–control studies (also known as 'two-gate' or 'multigate' designs). Prediction modelling studies were also eligible for inclusion.
- Participants – adults and/or children representative of the general population. Studies restricted to specific disease populations without healthy participants were excluded.
- Index test – any potential diagnostic indicator based on the definition provided previously.
- Reference standard – CD diagnosis, detected by one or more serological tests, including IgA/IgG tTG, EMA or DGP, and/or duodenal biopsy. All participants had to be tested for CD, including the control group participants.

Studies were included only if sufficient data could be extracted to construct cross-tabulations of the number of people with and the number without the diagnostic indicator against the number of people with and the number without CD, according to the reference standard.

We excluded studies published before 1997 (the year in which tTG testing was developed) to reduce variation in CD diagnostic tests.

Search strategy

The following databases were searched from 1997 to April 2021:

- MEDLINE® (National Library of Medicine, Bethesda, MD, USA)
- Embase® (Elsevier, Amsterdam, the Netherlands)
- Cochrane Library
- Web of Science™ (Clarivate™, Philadelphia, PA, USA)
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)
- the National Institutes of Health (NIH) Clinical Trials database.

The search strategy incorporated three main elements:

1. conditions (CD) + prognostic/predictive research filter[26,27]
2. conditions (CD) + all physical diseases/signs/symptoms (based on medical subject headings, Emtree) + 'CD' diagnosis
3. terms for high-risk populations (see *Appendix 1* for a detailed search strategy).[21]

Animal studies, case reports, letters, editorials and coeliac artery/trunk research were filtered out and a sensitive study design filter was applied. We also screened reference lists of the latest guidelines on CD and recent systematic reviews.

The results of the searches were downloaded and saved to an EndNote X9 library (Clarivate).

Study selection

Study selection was conducted in two stages using forms developed in Microsoft Access® (Microsoft Corporation, Redmond, WA, USA) that were piloted before use. Search results were exported from EndNote in a format that could be imported into Microsoft Access. At stage 1 of study selection, titles and abstracts were screened against the inclusion criteria to exclude papers that were clearly irrelevant. At the second stage, full texts identified as possibly relevant in the initial screening were assessed in detail and reasons for exclusion were documented. Both stages of study selection were performed independently by two reviewers, and disagreements about study eligibility were resolved through discussion or by consulting a third member of the review team.

Data collection process

Standardised data extraction forms were developed using Microsoft Access. These were piloted on a small sample of papers and adapted as necessary before use. Data extraction was performed by one reviewer and checked by a second, with disagreements resolved through discussion or referral to a third reviewer.

We extracted the following data from each included study:

- study characteristics
- participant characteristics
- details on the diagnostic indicator
- CD diagnostic tests used.

The results data were extracted as 2 × 2 tables of test results (numbers of true positives, false negatives, false positives and true negatives) for each diagnostic indicator against the reference standard of serological tests or biopsy. Two-by-two data were extracted at the biopsy cut-off point of Marsh grade 3a, if available; otherwise, any reported biopsy threshold was accepted.

Risk of bias

Risk of bias was assessed separately for each diagnostic indicator reported, so, for studies reporting on multiple indicators, risk of bias was assessed multiple times. We used the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool,[28] which includes domains covering participants, index test, reference standard and flow and timing. If at least one of the domains was rated as 'high risk', the study results were considered to be at high risk of bias; if all domains were judged as 'low risk', the study was considered as having a low risk of bias; otherwise, the study was considered to have an 'unclear' risk of bias. The content of the tool was tailored to the review. The following modifications were made to the QUADAS-2 risk-of-bias signalling questions:

- Owing to the broad research question and the expected heterogeneity between included studies, we did not formally assess applicability.
- We removed the following signalling questions, as these were not considered relevant to diagnostic indicator studies because the 'index test' is not a test but a diagnostic indicator and the reference standard is a diagnosis of CD –
    - 'Were the index test results interpreted without knowledge of the results of the reference standard?' (index test domain).
    - 'If a threshold was used, was it prespecified?' (index test domain).
    - 'Were the reference standard results interpreted without knowledge of the results of the index test?' (reference standard domain).
- We added the following signalling question –
    - 'Was the aim of the study to investigate this diagnostic indicator?' (index test domain).

The risk of bias was assessed by one reviewer and checked by a second as part of the data extraction process.

Synthesis of results

We present a narrative summary of the included studies, including a summary of the characteristics of the included studies that evaluated each diagnostic indicator (e.g. study design, population size, geographical location, year, population characteristics, diagnostic indicator details and CD diagnosis). We also describe the main methodological problems or biases that affected the studies.

The results were grouped by diagnostic indicator and age group. Diagnostic indicators were grouped based on discussion with clinical team members; for example, acid reflux symptoms included heartburn, dyspepsia and gastro-oesophageal reflux symptoms. If more than one indicator in each category was evaluated in one study (e.g. heartburn and dyspepsia), only one was included in the meta-analysis to avoid including the same individuals twice. In those cases, the broader term (e.g. dyspepsia over heartburn) or more prevalent diagnostic indicator was selected. Study populations were categorised as 'children' if the majority were children and none of the participants was aged > 21 years, and as 'adults' if the majority were adults with no participant aged < 15 years. All other populations were categorised as mixed-age groups.

We fitted a bivariate random-effects meta-analysis for each diagnostic indicator, in which we assumed binomial likelihoods for the numbers of true positives and true negatives.[29,30] Pooled estimates of sensitivity and specificity and estimates of the between-study standard deviation (SD) sensitivity and specificity on the logit scale ('tau') are reported. Per diagnostic indicator, we present study-specific and pooled estimates of sensitivity and specificity in coupled forest plots and summary receiver operating characteristic (SROC) plots, with 95% confidence ellipses and SROC curves.[20]

Summary results from each meta-analysis were also used to estimate positive predictive values (PPVs), that is the probability of CD given that an individual has each diagnostic indicator. To calculate these values, we assumed a prevalence of 1% of CD in the general population.[31,32] The 95% confidence intervals (CIs) around PPVs were computed using Monte Carlo simulation, simulating from a bivariate normal distribution for summary sensitivity and specificity on the logit scale. Negative predictive values are not informative in this context, because a sign, symptom or risk condition cannot be used in clinical practice to exclude CD; therefore, these are not reported.

Sensitivity analyses and subgroup analyses

Because we expected heterogeneity across studies in sensitivity and specificity as a result of variability in age groups (children vs. adults), method of CD diagnosis (biopsy and/or serology vs. serology only), and study design (single gate vs. multigate), we performed subgroup and sensitivity analyses on these study characteristics if subgroups contained at least five studies.

All statistical analyses were performed in R[33] (The R Foundation for Statistical Computing, Vienna, Austria) using lme4[34] and PropCIs[35] packages; forestplot,[36] flextable,[37] ggplot2,[38] mada[39] and ellipse[40] were used for tables and figures.

Deviations from the protocol

Owing to the size of the review and time constraints, it was not feasible to contact authors.

To make this review more manageable, we planned to extract data for diagnostic indicators with sufficient evidence only, which we defined as data on diagnostic indicators that are reported in five or more studies, unless our expert panel identified a diagnostic indicator as exceptionally promising. However, the expert panel agreed that most diagnostic indicators were potentially promising. To reduce bias in the process and to keep the review manageable, it was decided not to extract data on diagnostic indicators that were reported by fewer than five studies. We provide full references for all studies reporting on indicators for which we did not extract data. In addition, a post hoc sensitivity analysis was performed on the diagnostic indicator 'family history of CD' to restrict the analysis to first-degree relatives only.

As stated in the protocol,[21] we explored the possibility of adjusting for the imperfect accuracy of the serological tests in a Bayesian statistical framework, using informative prior distributions for the sensitivity and specificity of these tests based on our systematic review of the accuracy of serology tests for CD (see *Chapter 5*). However, this was not feasible because of the considerable variation in reference standards, including thresholds for reference standards, used across studies.

Results of assessment of diagnostic accuracy of indicators

We identified 12,027 records, after deduplication, through searching scientific databases and screening the reference lists of four recent guidelines on CD[9–11,41,42] and 22 systematic reviews. Of these, 709 records were selected for full-text assessment, of which 241 studies fulfilled the inclusion criteria. These studies contained 369 reports of 90 distinct diagnostic indicators. Table S1 (see *Report Supplementary Material 1*) provides a list of diagnostic indicators (including study references) for which we did not extract data because they reported on a rare indicator (reported by fewer than five studies). We included 183 studies reporting on 25 distinct indicators in our meta-analysis (see *Appendix 2*, *Figure 26*).

Study characteristics

The included diagnostic indicators consisted of seven symptoms, 17 risk conditions and family history (see *Appendix 3*, *Table 25*, and *Appendix 4*, *Tables 26–51*). The symptoms that were most often investigated as diagnostic indicators were abdominal pain ($n = 12$) and diarrhoea ($n = 12$), while type 1 diabetes ($n = 31$) and thyroid disease ($n = 23$) were the most commonly studied risk conditions. Studies investigating

symptoms associated with CD predominantly used a cohort or cross-sectional design, using a serological test to detect CD. Studies looking at risk conditions mainly used case–control designs, that is, people with the diagnostic indicator were compared with a healthy control group without the diagnostic indicator. Most studies included adult participants, although many diagnostic indicators were also studied in a population of children or a mixed population.

Although sample sizes for each meta-analysis ranged between 1004 and 55,500 participants, some meta-analyses were based on a small number of CD participants, as prevalence was often low. For instance, in the case of multiple sclerosis and systemic lupus erythematosus, estimates of sensitivity are based on only 12 and nine people with CD, respectively.

Risk of bias

Several studies reported more than one diagnostic indicator, resulting in 281 risk-of-bias judgements. Most studies had methodological issues, and only one study was judged as having a low overall risk of bias (see *Appendix 5*, *Figure 27*). In total, only 19 study reports were judged to be at low risk of bias regarding patient selection. The main source of potential bias in patient selection was the use of a case–control study design. The index test domain was judged to be at low risk of bias if it was the study's main aim to investigate the diagnostic indicator of interest, which was the case for most studies. In total, 167 study reports on diagnostic indicators were judged to have a high risk of bias for the reference standard. This was mainly driven by studies using serology tests without biopsy confirmation to determine whether or not participants had CD; this risks misclassifying participants as having or not having CD. Flow and timing were judged to be at high risk of bias in studies that did not use the same combination of diagnostic tests for CD for all participants (reference standard), for example in studies in which a biopsy was performed only in participants who had a positive serology test result.

Accuracy of diagnostic indicators to detect coeliac disease

We found large variation in sensitivity, specificity and PPV estimates between studies for most diagnostic indicators (*Figure 1*) (see *Appendix 6*, *Figures 28–51*; see also table S2 and figure S1 in *Report Supplementary Material 1*). Estimates of sensitivity were particularly variable, often ranging from 0% to almost 100%, owing to very small numbers of CD participants for some indicators.

The PPVs for the symptoms included in this review are similar to the baseline CD prevalence, with 95% CIs providing no evidence that the presence of any of these symptoms increases the chance that an individual has CD beyond the levels found in the general population (see *Figure 1*).

Figure S1 (see *Report Supplementary Material 1*) shows meta-analysis results in receiver operating characteristic (ROC) space. A diagnostic indicator with a SROC curve closely following the diagonal line is no better at predicting CD than a coin toss, which is approximately the case for all symptoms.

Of the risk conditions, dermatitis herpetiformis had the highest estimated sensitivity, specificity and PPV (the estimated PPV at 1% prevalence of CD was 29%, 95% CI 3% to 72%). However, the uncertainty around these estimates was substantial, that is the 95% CIs were very wide. In addition, dermatitis herpetiformis is a rare condition, so it will be a clinically useful diagnostic indicator in only a minority of cases. We estimated PPVs of > 2% for migraine, anaemia, type 1 diabetes, osteoporosis and chronic liver disease. These estimates were relatively precise for anaemia, type 1 diabetes, osteoporosis and chronic liver disease, but there was considerable uncertainty for migraine. People with thyroid disease, subfertility or recurrent pregnancy loss, or IBS were 1.5–2 times more likely to have CD than the general population, with 95% CIs lying entirely above the population prevalence of 1%. Although the estimated PPVs of psoriasis, epilepsy, inflammatory bowel disease, systemic lupus erythematosus, fracture, arthritis and type 2 diabetes suggest an increased likelihood of CD among people with these conditions, there was considerable uncertainty in these estimates. The 95% CIs crossed or touched the line of population prevalence, indicating that the likelihood of CD may be similar to that of the general population. We found no evidence of an increased likelihood of CD among people with multiple sclerosis (see *Figure 1*).

Diagnostic indicator	Studies (*n*)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Symptoms					
Abdominal pain	12	255	14,345	759	33,092
Diarrhoea	13	161	6384	965	47,990
Constipation	12	101	7217	842	46,126
Acid reflux symptoms	10	54	3169	480	8489
Bloating or abdominal distension	6	64	5809	560	26,261
Weight loss	5	52	4722	769	26,196
Vomiting and nausea	7	48	4898	387	39,604
Risk conditions					
Dermatitis herpetiformis	5	64	36	515	814
Migraine	5	10	375	32	2061
Anaemia	17	153	2346	562	10,416
Type 1 diabetes	31	699	6047	650	19,239
Osteoporosis	9	44	1777	918	17,479
Chronic liver disease	11	38	2144	410	6090
Psoriasis	6	34	498	10	585
Thyroid disease	23	212	4752	871	21,196
Epilepsy	12	69	3065	436	7147
Inflammatory bowel disease	6	20	1163	12	1691
Systemic lupus erythematosus	6	8	532	1	463
IBS	18	161	4962	681	12,642
Subfertility or recurrent pregnancy loss	16	185	3418	623	8464
Fracture	8	81	2179	468	22,013
Arthritis	15	67	2045	475	8158
Type 2 diabetes	6	34	972	76	7117
Multiple sclerosis	5	7	501	5	573
Genetic predisposition					
Family history of CD	13	332	7021	340	24,134

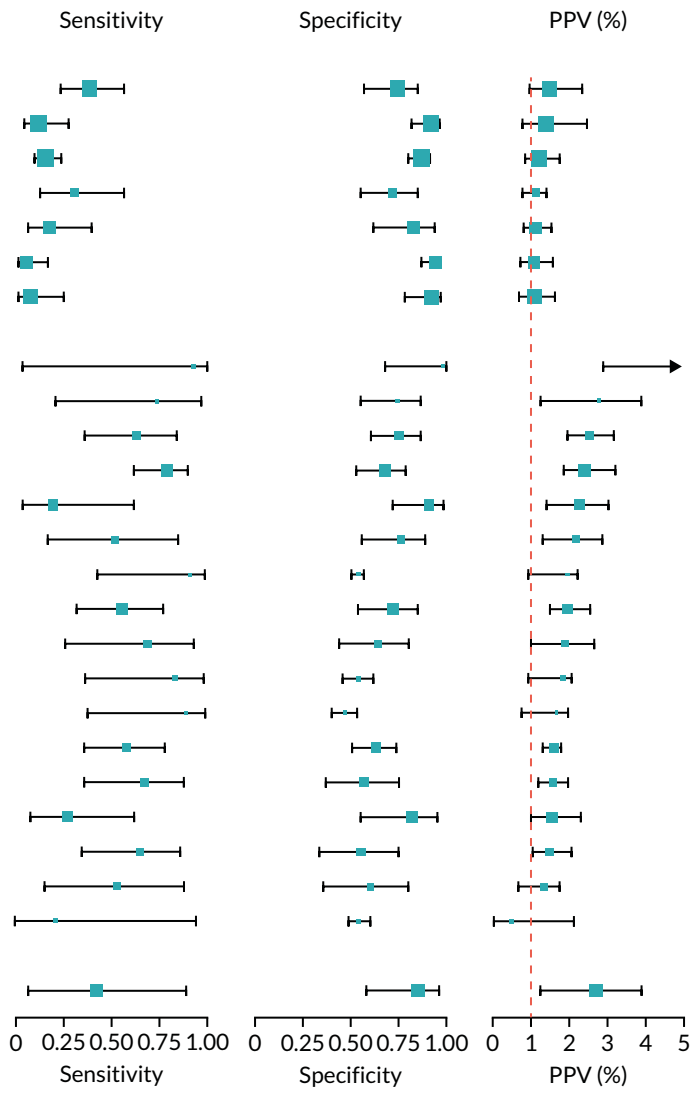

FIGURE 1 Sensitivity, specificity and PPVs. Meta-analysis results are shown per diagnostic indicator. PPVs were calculated for a population with a CD prevalence of 1% (red dotted line) using the estimated sensitivities and specificities from the meta-analyses. Diagnostic indicators are ordered from high to low PPV per diagnostic indicator group. The area of the box size is proportional to the total number of participants. Negative predictive values are not shown because these diagnostic indicators should not be used to rule out CD. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Similarly, arthritis, fracture and type 2 diabetes appear to have no diagnostic ability when judging sensitivity and specificity in ROC space (see figure S1 in *Report Supplementary Material 1*). For multiple sclerosis, systemic lupus erythematosus, psoriasis and inflammatory bowel disease, there was not enough evidence to estimate a reliable SROC curve. For chronic liver disease, epilepsy, migraine, IBS, and dermatitis herpetiformis, there was substantial uncertainty in summary estimates because of a high level of variation between the study estimates. The SROC plots for type 1 diabetes, anaemia, subfertility or recurrent pregnancy loss, thyroid disease and osteoporosis suggest a greater accuracy in predicting CD than a coin toss.

People with a family history of CD were 2.7% (95% CI 1.2 to 3.0%) more likely to have CD than the general population.

Subgroup and sensitivity analyses

There were sufficient data on five diagnostic indicators to stratify the meta-analyses by age group (see *Appendix 7*, *Figure 52*; see also table S3 in *Report Supplementary Material 1*). Estimated PPVs were similarly low, at around 1%, for abdominal pain, arthritis, constipation and diarrhoea for adults and children. The results suggest that arthritis may be more predictive of CD in children than in adults, and abdominal pain and constipation may be more predictive of CD in adults than in children. The PPV for type 1 diabetes appeared to be higher for adults [3.4% (95% CI 1.9% to 5.6%)] than for children or mixed populations [1.8% (95% CI 1.4% to 2.3%) and 2.1% (95% CI 1.6% to 2.9%), respectively]. However, each of these differences should be interpreted with caution because the CIs overlap.

There were sufficient data on seven diagnostic indicators to stratify the analysis on CD diagnosis, comparing studies that used a serology-only approach with studies that included a confirmation duodenal biopsy (see *Appendix 7*, *Figure 52*; see also table S3 in *Report Supplementary Material 1*). Estimated PPVs were similar between the subgroups.

A sensitivity analysis was performed restricted to studies using a cohort or cross-sectional design for abdominal pain, anaemia, bloating or abdominal distension, constipation and diarrhoea (see *Appendix 8*, *Figure 53*; see also table S4 in *Report Supplementary Material 1*). Although case–control studies are more prone to bias than cohort studies, removing case–control studies did not affect the sensitivity, specificity or PPV estimates among these diagnostic indicators. It was not possible to perform a sensitivity analysis restricted to studies with a low risk of bias, because all included studies were judged to be at an overall high risk of bias.

Finally, a post hoc sensitivity analysis was performed on the diagnostic indicator ‘family history of CD’, restricted to studies that included only first-degree relatives. This increased the estimated PPV from 2.7% (95% CI 1.2% to 3.9%) to 3.0% (95% CI 1.6% to 3.7%), although the CIs overlap.

Chapter 4 Prediction rule for coeliac disease diagnosis

This chapter describes the development and internal validation of diagnostic prediction models for men, women and children in a routinely collected primary care data set to estimate the probability of having CD. We also describe the development of a model for children in a birth cohort, with external validation in the primary care data set. The aim of each prediction model is to help clinicians in primary care decide whether or not a patient should be offered a serological test for CD based on their pre-existing conditions and current/recent symptoms. To demonstrate the potential clinical usefulness of each model, we present the PPVs and percentage of CD patients missed at different thresholds.

Prediction modelling methods

Protocol

An analysis protocol was developed and published online.[43] We followed methodological recommendations from Steyerberg.[44] This chapter follows reporting guidelines for multivariable models described in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[45]

Model development

Sources of data

Model development was performed in Clinical Practice Research Datalink (CPRD) GOLD.[46] CPRD GOLD contains anonymised patient electronic health records collected from UK general practices using the Vision® software system (In Practice Systems Ltd, London, UK), with > 20 million 'acceptable' patients currently (with research quality data based on CPRD metrics), of whom 9 million are eligible for linkage with hospital records and national statistics.[46,47] The included patients are broadly representative of the UK general population regarding age, sex and ethnicity. The CPRD GOLD data set was linked to Hospital Episode Statistics (HES) and the 2019 English Index of Multiple Deprivation (IMD).[48]

The target population included permanently registered 'acceptable' patients, and only up-to-standard (UTS) follow-up time was considered. UTS is a practice-based quality metric based on the continuity of recording and the number of recorded deaths.[46] Patients from general practices that were UTS for at least 12 months prior to diagnosis were included.

The follow-up period was defined as the time between the study start and end dates. The study start was the latest of the start of linked data coverage, the date of patient registration with the practice and the UTS date of that practice; the study end was the earliest of the last date for linked data, the date of patient transfer-out from practice, the date of patient's death (according to CPRD death date) or the last date of data collection from that practice.

Study design

We used a nested case–control design. Cases were defined as individuals with one or more clinical codes related to CD.[4] Table S5 (see *Report Supplementary Material 1*) shows the Read codes and medcodes used to identify patients with CD in CPRD GOLD. Read codes are a coded thesaurus of clinical terms that have been used in the NHS since 1985. Medcodes are specific to CPRD GOLD. Cases with a diagnosis of dermatitis herpetiformis were included, but not those with dermatitis herpetiformis alone. We assigned a date of diagnosis (the 'index date') to each case corresponding to the date of their first record of CD. For cases with more than one CD code, the earliest was considered as the date of disease diagnosis. All CD cases within the target population were included.

All remaining patients in the target population (individuals without any of the CD codes) were selected as potential controls. From these, we excluded patients with a record of gluten-free prescriptions, dermatitis herpetiformis or gluten sensitivity diagnosis to reduce the risk of including undiagnosed CD patients in the control group.[4,49,50]

Cases and controls were matched using a 1 : 4 ratio on age group (aged < 18 or ≥ 18 years), general practice and availability of linkages. Controls inherited the index date of their matched case, and follow-up time between the case's start and end dates only was considered. We matched by age group (adult vs. child) to ensure that there were sufficient child controls to allow an efficient study design.

The data set was split into separate data sets for children, women and men to develop three separate diagnostic prediction models. The next steps describing model development were performed separately for each data set.

We performed descriptive analyses of all variables and tested the statistical difference between cases and controls using Welch's two-sample *t*-test for continuous variables and Pearson's chi-squared test with Yates' continuity correction for categorical variables.

Sample size

We performed a sample size calculation according to Riley *et al.*[51] To consider 40 candidate predictors in each model, we estimated a minimum total sample size of 4303.

Model specification

Identifying candidate diagnostic indicators

Diagnostic indicators identified in the systematic review presented in *Chapter 4* were considered for inclusion in the prediction models. To avoid the effect of potential publication bias, we also included indicators suggested by our clinical experts and indicators listed in national and international guidelines for CD,[9–11] which are based on both evidence and expert opinion. See *Appendix 9*, *Table 52*, for the list of candidate diagnostic indicators, their definitions and how they were identified. The *International Classification of Primary Care*, 2nd edition (ICPC-2), definitions were used when available. The ICPC-2 is an international classification for systematically capturing and ordering clinical information in primary care. It was developed by the World Organization of Family Doctors' International Classification Committee and was last updated in 2015.[52] Dermatitis herpetiformis could not be included as an indicator because it was an exclusion criterion for the control cohort. Sex was considered as an indicator in the children's model and age was considered in all models, because both are important demographic factors.

Code list development

When possible, existing code lists were used to define diagnostic indicators. If these were not available, code lists were developed with the clinicians on our team, who identified all relevant terms and synonyms for each indicator, and the CPRD code browser tool was used to identify all relevant codes. Each code list was checked by at least two clinicians (see table S6 in *Report Supplementary Material 1*).

Missing data

The presence of a diagnostic indicator was defined by the presence of one or more specific medical codes. It was not possible to determine whether or not a code was 'missing', because if these codes were absent from a patient record we assumed that the patient did not have the indicator, in the case of disease diagnoses, or that the indicator was not considered sufficiently important to have been recorded by the general practitioner (GP), in the case of symptoms. This will be correct for most indicators unless the indicator was either underdiagnosed or under-reported (such as symptoms). Missingness could be investigated only for sex, ethnicity and age; however, no data were missing for these variables.

Transformations and categorisations of variables

Age was included in the model as a linear term (in years), because the risk of being diagnosed (in adulthood) appears to decrease linearly with age.[53] All risk conditions were coded as 1 or 0 for having or not having the disease at any time point prior to the index date.

Diagnostic indicators that can resolve and return (including GI symptoms; weight loss; fatigue; abnormal liver function test results; mouth ulcers; irritability; iron, vitamin B_{12} or folate deficiency; fractures; and headaches or migraines) were included as binary variables, and coded as 1 if the event occurred within 10 years prior to the index date. Diagnostic indicators that could vary substantially over time (including GI symptoms, fatigue, irritability, mouth ulcers, fractures, and migraine or headaches) were also included as counts of the number of times these symptoms were recorded in the CPRD. Because these counts were highly skewed, we collapsed groups with the highest counts if they were higher than the third quantile (e.g. 0, 1, 2, 3+). For each of these indicators, we considered a count of the number of times these symptoms were recorded in the CPRD within 1, 2 and 10 years prior to the index date.

A variable for 'first-degree relative with CD' was created using the famnum variable in CPRD GOLD, which is a number assigned based on the first line of a patient's home address at registration. Because famnum is not unique across all general practices, a unique variable was created combining famnum and general practice identification (ID). We counted people as a first-degree relative only if they had the same famnum and were registered at the same general practice as a case, and were either aged > 25 years and differed in age from the case by < 15 years (to include all children and students, assuming that students were still registered with their parents' general practices) or differed in age from the case by > 15 years (to exclude spouses).

Model selection

We fitted a logistic regression model with CD as the outcome and all candidate diagnostic indicators as potential explanatory factors. We used the elastic net method combined with bootstrapping for variable selection. The elastic net logistic regression combines ridge and least absolute shrinkage and selection operator (LASSO) regressions (regression coefficients are estimated with a combination of L_1 and L_2 penalties) and performs both shrinkage and variable selection.[44] It does this by including a regularisation penalty (lambda) and a mixing parameter (alpha), whereby 0 results in ridge and 1 in LASSO regression. Optimal alpha and lambda values were determined by testing 100 different lambda values at 18 different alpha values (increasing from 0.1 to 0.9). For each combination of alpha and lambda, 20 fivefold cross-validations were performed. We selected the alpha–lambda combination that produced the model with the highest *c*-statistic [i.e. area under the receiver operating characteristic (AUROC)].

The model with optimised L_1 and L_2 penalties was performed on 200 bootstrap samples. Indicators were selected if their coefficient was non-zero in the majority of bootstrap samples. To be relatively inclusive at this stage, we set the threshold at 75%. If more than one of the three alternative counts for the same symptom was selected (frequency of indicator over the last 1, 2 or 10 years), the count with the highest median coefficient was included in the final model. As candidate diagnostic indicators had been selected based on some evidence of a positive relationship with CD, if we estimated an inverse relationship with CD in these data, we assumed that this was due to noise in this specific data set and excluded the indicator.

We did not allow indicators with strong prior evidence of an association with CD to drop out of the model during variable selection, regardless of their estimated coefficients and *p*-values. These were the following five indicators that were found to be most predictive in our meta-analyses (see *Chapter 3*): family history of CD, anaemia, type 1 diabetes, osteoporosis and thyroid disease.

Model estimation

We refitted the elastic net logistic regression model using the set of included indicator variables to determine the final coefficient estimates at the optimal alpha and lambda values.

To estimate the intercept, we adjusted for sampling frequency by recreating a population with the CD prevalence of the original cohort.[54,55] CD prevalence in the general population is estimated to be 1%, so we inflated the control group by random sampling to a case-to-control ratio of 1 : 99. We refitted the elastic net logistic regression model on this inflated data set to determine the intercept with the optimal alpha and lambda values.

Model performance

We estimated the model performance on the development data set (apparent model performance) using measures of both discrimination and calibration.[56]

Discrimination is the ability of the model to distinguish between those with and those without CD, also known as the concordance or *c*-statistic, and is identical to the AUROC curve, in which sensitivity is plotted against 1 – specificity. If the *c*-statistic is 0.5, the model has no predictive ability; if the *c*-statistic is 1, the model has perfect prediction.

Calibration is the agreement between predictions and observed outcomes. Calibration was assessed graphically using the calibration plot, which plots the predicted risk against the observed risk using centile population groups. In the case of a perfect prediction, the intercept is 0 and the slope is 1. The calibration statistics were adjusted for sampling frequency.

We assessed amount of variability explained by model variables with the Nagelkerke R^2 score and the overall (statistical) model fit with the Brier score.[44]

Internal validation

We performed internal validation of the model using bootstrapping methods.[56] We fitted the final model using elastic net regression with the predefined optimal lambda and alpha values on 1000 bootstrap samples to estimate the median of each coefficient and calculate empirical CIs around the coefficients. The elastic net regression uses shrinkage to adjust for overfitting and optimism. Using the 1000 model fits, we calculated the median and empirical CIs for performance statistics (R^2, Brier score and *c*-statistic). To estimate the median and empirical CIs for the intercept and calibration statistics, we inflated the control group by random sampling to a case-to-control ratio of 1 : 99 for each bootstrapped sample and then fitted the final model on this data set.

Sensitivity analyses

Data since 1997

We performed a sensitivity analysis restricted to patients diagnosed after 1997, because it was in this year that IgA tTG tests, which are now the preferred serological test for screening for CD, were first developed. Model development, as described previously, was repeated on this data set. We used the *c*-statistic to determine whether or not model performance was improved using this data set.

Linkages: including ethnicity and deprivation

Data sets were linked to HES and 2019 IMD[48] data to consider ethnicity and deprivation, which are not measured in the CPRD, as additional candidate diagnostic indicators. We repeated the model development, as described previously, on the subset of patients who were successfully linked to HES and 2019 IMD[48] data. Ethnicity was transformed to a binary variable (white or non-white). Deprivation deciles were used as deprivation score, where 1 represents the highest levels of deprivation and 10 the lowest. We used the *c*-statistic to determine whether or not model performance was improved by including ethnicity and deprivation.

Clinical usefulness

We calculated the sensitivity and specificity of the prediction models for different thresholds of predicted CD risk. The thresholds were chosen based on the PPVs of the prediction model and the percentage of CD patients missed at that threshold (i.e. the percentage of false negatives among CD patients). The pre-test probability for the general population is 1%, so we specified model thresholds that corresponded to PPVs of 1.5%, 2%, 5%, 10% and 20%. We also report the percentage of CD patients missed at each threshold, that is the percentage of people with CD who would not be picked up by the prediction model.

External validation

Sources of data

External validation was performed in CPRD Aurum,[57] which is another primary care data set provided by the CPRD. This contains electronic health records from general practices in England using the EMIS Web software system (EMIS Health, Leeds, UK). CPRD Aurum is a larger data set than CPRD GOLD: it contains > 40 million research-acceptable patients, of whom 37 million are eligible for linkages with hospital records and national statistics.[58] The included patients are broadly representative of the UK general population regarding age, sex, deprivation and geographical spread.

The cohort was defined as described for CPRD GOLD, with the only difference that CPRD Aurum does not report UTS dates, so this could not be taken into account when defining study start and end dates. Patients with records in both the CPRD GOLD and the CPRD Aurum data sets, for instance because their general practice switched software systems or a patient moved to a different general practice that used another software, were removed from the Aurum data set.

Diagnostic indicators and code lists

The code lists developed for CPRD GOLD were mapped to medical codes used in Aurum (medcode ID) using the code browser tool from the CPRD; Read codes were mapped directly to medcode IDs, as well as indirectly via Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) concept IDs, to capture all codes related to the Read codes. The mapped lists were checked by hand before use (see table S7 in *Report Supplementary Material 1*).

The famnum variable that was used in CPRD GOLD to derive the first-degree relatives indicator does not exist in Aurum. To account for this, we present all model performance measures as a range for individuals with and individuals without a first-degree relative with CD.

Validation

Predictions were made for the patients in Aurum using the intercepts and coefficients from the models developed in CPRD GOLD. Model performance statistics were calculated as described previously.

Model development in the Avon Longitudinal Study of Parents and Children

Sources of data

We requested individual participant data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study established in 1990.[59–61] A substudy of the ALSPAC, published in 2004,[2] involved serological testing for CD in 5470 children aged 7.5 years. Ethics approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).[62] Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

The ALSPAC has not collected information on all candidate diagnostic indicators that were considered in the CPRD model, so it was not possible to validate the CPRD model in this data set. The study website[63] contains details of all the data that are available through a fully searchable data dictionary and variable search tool.

Model specification

Candidate diagnostic indicators for the ALSPAC model were selected based on the results from the final model developed in CPRD GOLD. The prevalence of indicators among children with and children without CD was compared using Fisher's exact test (categorical indicators) and Welch's two-sample *t*-test (continuous indicators). Univariable associations between candidate indicators and CD were estimated using Firth logistic regression for rare events to overcome problems of perfect prediction between outcome and indicators.[64,65] Owing to the small number of cases in this cohort, it was not considered appropriate to fit multivariable models.

Avon Longitudinal Study of Parents and Children: missing data

As it is possible for candidate indicators collected in the ALSPAC to be incomplete (e.g. because of non-response to questionnaire items), missingness was investigated in all indicators. If indicators were partially missing, when there were sufficient data, we considered imputing missing values using multiple imputation by chained equations, assuming values were missing at random conditional on observed covariates.

Deviations from protocol

In the CPRD model development, we used logistic regression instead of conditional logistic regression because cases and controls were matched on very few characteristics, namely being a child or an adult and general practice. Interaction terms were not considered as they are rarely important for clinical prediction models.[66]

We planned to validate the CPRD model in children in the ALSPAC cohort. However, this was not possible because many of the selected indicators in the CPRD model were not recorded in the ALSPAC, and, among the indicators that were available, there was a lot of missingness.

Results

Clinical Practice Research Datalink participants

Appendix 10, *Figure 54*, shows the patient flow diagrams for the CPRD development data set and the external validation data set. Cases and controls had an average follow-up time of 7 years prior to CD diagnosis [median 7 years, interquartile range (IQR) 3–11 years, range 1–31 years].

Table 2 describes the characteristics of the participants and the prevalence of selected indicators in the development data set and the external validation data set for children, women and men. In both data sets, the prevalence of CD was significantly higher among girls than boys in the cohort of children, with almost two-thirds of CD patients being girls. The median age and age ranges were similar between CD patients and controls in the cohort of children in the development data set; however, in the validation data set, children with CD were, on average, 1 year younger than controls. In the development data set for women, the median age was 49 years for both cases and controls. In the external validation data set, the median age was similar, at 47 years, although cases were, on average, 1 year younger than controls. In contrast to the data sets for children and women, in both data sets for men, cases were significantly older than controls, with a median age of 55 years for cases and 47 years for controls. On average, CD male patients were 8 and 7 years older than controls in the development and validation data sets, respectively.

TABLE 2 Cohort of children, women and men: characteristics

	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
Cohort and characteristic	**Control**	**CD**	***p*-value**	**Overall**	**Control**	**CD**	***p*-value**	**Overall**
Children	***(N = 12,948)***	***(N = 3237)***		***(N = 16,185)***	***(N = 28,131)***	***(N = 7033)***		***(N = 35,164)***
Age (years)								
Mean (SD)	9.04 (4.62)	8.89 (4.77)	0.127	9.01 (4.65)	8.96 (4.61)	8.66 (4.74)	< 0.001	8.90 (4.64)
Median (minimum, maximum)	9.00 (1.00, 17.0)	9.00 (1.00, 17.0)		9.00 (1.00, 17.0)	9.00 (1.00, 17.0)	8.00 (1.00, 17.0)		9.00 (1.00, 17.0)
Sex, *n* (%)								
Male	6862 (53.0)	1249 (38.6)	< 0.001	8111 (50.1)	15024 (53.4)	2702 (38.4)	< 0.001	17,726 (50.4)
Female	6086 (47.0)	1988 (61.4)		8074 (49.9)	13107 (46.6)	4331 (61.6)		17,438 (49.6)
Ethnicity, *n* (%)								
Non-white	438 (3.4)	98 (3.0)	0.004	536 (3.3)	686 (2.4)	156 (2.2)	< 0.001	842 (2.4)
White	3816 (29.5)	1205 (37.2)		5021 (31.0)	3478 (12.4)	1103 (15.7)		4581 (13.0)
Missing	8694 (67.1)	1934 (59.7)		10,628 (65.7)	23,967 (85.2)	5774 (82.1)		29,741 (84.6)
Deprivation (IMD 2015[67] quintiles), *n* (%)								
1	1104 (8.5)	385 (11.9)	0.059	1489 (9.2)	1532 (5.4)	391 (5.6)	0.057	1923 (5.5)
2	896 (6.9)	270 (8.3)		1166 (7.2)	1154 (4.1)	310 (4.4)		1464 (4.2)
3	871 (6.7)	264 (8.2)		1135 (7.0)	1000 (3.6)	280 (4.0)		1280 (3.6)
4	742 (5.7)	219 (6.8)		961 (5.9)	836 (3.0)	188 (2.7)		1024 (2.9)
5	641 (5.0)	165 (5.1)		806 (5.0)	858 (3.1)	185 (2.6)		1043 (3.0)
Missing	8694 (67.1)	1934 (59.7)		10,628 (65.7)	22,751 (80.9)	5679 (80.7)		28,430 (80.8)
Anaemia, *n* (%)								
Present	46 (0.4)	188 (5.8)	< 0.001	234 (1.4)	25 (0.1)	84 (1.2)	< 0.001	109 (0.3)

continued

TABLE 2 Cohort of children, women and men: characteristics (*continued*)

	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
Cohort and characteristic	**Control**	**CD**	***p*-value**	**Overall**	**Control**	**CD**	***p*-value**	**Overall**
Arthritis, *n* (%)								
Present	5 (0.0)	7 (0.2)	0.003	12 (0.1)	5 (0.0)	3 (0.0)	0.426	8 (0.0)
Delayed puberty, *n* (%)								
Present	1 (0.0)	5 (0.2)	< 0.001	6 (0.0)	2 (0.0)	2 (0.0)	0.382	4 (0.0)
Down syndrome, *n* (%)								
Present	6 (0.0)	18 (0.6)	< 0.001	24 (0.1)	2 (0.0)	15 (0.2)	< 0.001	17 (0.0)
Failure to thrive, *n* (%)								
Present	52 (0.4)	84 (2.6)	< 0.001	136 (0.8)	21 (0.1)	31 (0.4)	< 0.001	52 (0.1)
Fatigue, *n* (%)								
Present	210 (1.6)	253 (7.8)	< 0.001	463 (2.9)	165 (0.6)	150 (2.1)	< 0.001	315 (0.9)
Fatigue (count, 1 year), *n* (%)								
Once	53 (0.4)	130 (4.0)	< 0.001	183 (1.1)	34 (0.1)	48 (0.7)	< 0.001	82 (0.2)
Twice	5 (0.0)	17 (0.5)		22 (0.1)	8 (0.0)	14 (0.2)		22 (0.1)
Three times	0 (0)	11 (0.3)		11 (0.1)	2 (0.0)	8 (0.1)		10 (0.0)
First-degree relative with CD, *n* (%)								
Present	98 (0.8)	496 (15.3)	< 0.001	594 (3.7)	NR	NR		NR
GI symptoms, *n* (%)								
Present	3684 (28.5)	1924 (59.4)	< 0.001	5608 (34.6)	1371 (4.9)	794 (11.3)	< 0.001	2165 (6.2)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
GI symptoms (count, 1 year), *n* (%)								
Once	785 (6.1)	588 (18.2)	< 0.001	1373 (8.5)	293 (1.0)	218 (3.1)	< 0.001	511 (1.5)
Twice	192 (1.5)	294 (9.1)		486 (3.0)	82 (0.3)	126 (1.8)		208 (0.6)
Three times	55 (0.4)	154 (4.8)		209 (1.3)	24 (0.1)	60 (0.9)		84 (0.2)
Four times	52 (0.4)	203 (6.3)		255 (1.6)	39 (0.1)	98 (1.4)		137 (0.4)
IBS, *n* (%)								
Present	20 (0.2)	29 (0.9)	< 0.001	49 (0.3)	6 (0.0)	12 (0.2)	< 0.001	18 (0.1)
IgA deficiency, *n* (%)								
Present	0 (0)	4 (0.1)	< 0.001	4 (0.0)	1 (0.0)	4 (0.1)	0.005	5 (0.0)
Iron, vitamin B_{12} or folate deficiency, *n* (%)								
Present	8 (0.1)	35 (1.1)	< 0.001	43 (0.3)	8 (0.0)	24 (0.3)	< 0.001	32 (0.1)
Mood disorders, *n* (%)								
Present	256 (2.0)	143 (4.4)	< 0.001	399 (2.5)	91 (0.3)	59 (0.8)	< 0.001	150 (0.4)
Type 1 diabetes, *n* (%)								
Present	16 (0.1)	275 (8.5)	< 0.001	291 (1.8)	11 (0.0)	87 (1.2)	< 0.001	98 (0.3)
Thyroid disorders, *n* (%)								
Present	16 (0.1)	61 (1.9)	< 0.001	77 (0.5)	12 (0.0)	21 (0.3)	< 0.001	33 (0.1)
Turner syndrome, *n* (%)								
Present	0 (0)	8 (0.2)	< 0.001	8 (0.0)	1 (0.0)	5 (0.1)	< 0.001	6 (0.0)
Weight loss, *n* (%)								
Present	23 (0.2)	93 (2.9)	< 0.001	116 (0.7)	8 (0.0)	22 (0.3)	< 0.001	30 (0.1)

continued

TABLE 2 Cohort of children, women and men: characteristics (*continued*)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
Women	***(N = 37,079)***	***(N = 12,051)***		***(N = 49,130)***	***(N = 77,422)***	***(N = 26,164)***		***(N = 103,586)***
Age (years)								
Mean (SD)	49.5 (17.0)	49.7 (17.2)	0.313	49.6 (17.0)	48.5 (17.0)	47.4 (17.6)	< 0.001	48.2 (17.2)
Median (minimum, maximum)	49.0 (18.0, 111)	49.0 (18.0, 104)		49.0 (18.0, 111)	47.0 (18.0, 108)	46.0 (18.0, 99.0)		47.0 (18.0, 108)
Ethnicity, *n* (%)								
Non-white	807 (2.2)	212 (1.8)	< 0.001	1019 (2.1)	1262 (1.6)	399 (1.5)	< 0.001	1661 (1.6)
White	12,286 (33.1)	4612 (38.3)		16,898 (34.4)	11,210 (14.5)	4496 (17.2)		15,706 (15.2)
Missing	23,986 (64.7)	7227 (60.0)		31,213 (63.5)	64,950 (83.9)	21,269 (81.3)		86,219 (83.2)
Deprivation (IMD 2015 quintiles), *n* (%)								
1	3199 (8.6)	1262 (10.5)	0.174	4461 (9.1)	4255 (5.5)	1424 (5.4)	0.276	5679 (5.5)
2	2939 (7.9)	1077 (8.9)		4016 (8.2)	3696 (4.8)	1254 (4.8)		4950 (4.8)
3	2761 (7.4)	1001 (8.3)		3762 (7.7)	2975 (3.8)	991 (3.8)		3966 (3.8)
4	2292 (6.2)	819 (6.8)		3111 (6.3)	2642 (3.4)	966 (3.7)		3608 (3.5)
5	1902 (5.1)	665 (5.5)		2567 (5.2)	2146 (2.8)	702 (2.7)		2848 (2.7)
Missing	23,986 (64.7)	7227 (60.0)		31,213 (63.5)	61,708 (79.7)	20,827 (79.6)		82,535 (79.7)
Anaemia, *n* (%)								
Present	1038 (2.8)	1969 (16.3)	< 0.001	3007 (6.1)	484 (0.6)	968 (3.7)	< 0.001	1452 (1.4)
Cardiovascular disease, *n* (%)								
Present	1601 (4.3)	883 (7.3)	< 0.001	2484 (5.1)	602 (0.8)	317 (1.2)	< 0.001	919 (0.9)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
Chronic liver disease, *n* (%)								
Present	376 (1.0)	253 (2.1)	< 0.001	629 (1.3)	233 (0.3)	180 (0.7)	< 0.001	413 (0.4)
Down syndrome, *n* (%)								
Present	5 (0.0)	5 (0.0)	0.132	10 (0.0)	4 (0.0)	4 (0.0)	0.229	8 (0.0)
Epilepsy, *n* (%)								
Present	194 (0.5)	116 (1.0)	< 0.001	310 (0.6)	109 (0.1)	46 (0.2)	0.24	155 (0.1)
Fatigue, *n* (%)								
Present	4638 (12.5)	3027 (25.1)	< 0.001	7665 (15.6)	1755 (2.3)	1165 (4.5)	< 0.001	2920 (2.8)
Fatigue (count, 1 year), *n* (%)								
Once	945 (2.5)	953 (7.9)	< 0.001	1898 (3.9)	333 (0.4)	341 (1.3)	< 0.001	674 (0.7)
Twice	145 (0.4)	174 (1.4)		319 (0.6)	86 (0.1)	118 (0.5)		204 (0.2)
Three times	38 (0.1)	73 (0.6)		111 (0.2)	56 (0.1)	79 (0.3)		135 (0.1)
First-degree relative with CD, *n* (%)								
Present	108 (0.3)	416 (3.5)	< 0.001	524 (1.1)	NR	NR		NR
Fractures (count, 1 year), *n* (%)								
Once	320 (0.9)	202 (1.7)	< 0.001	522 (1.1)	139 (0.2)	65 (0.2)	< 0.001	204 (0.2)
Twice	169 (0.5)	84 (0.7)		253 (0.5)	92 (0.1)	60 (0.2)		152 (0.1)
GI symptoms, *n* (%)								
Present	12,364 (33.3)	6994 (58.0)	< 0.001	19,358 (39.4)	4520 (5.8)	2603 (9.9)	< 0.001	7123 (6.9)

continued

TABLE 2 Cohort of children, women and men: characteristics (*continued*)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
GI symptoms (count, 1 year), *n* (%)								
Once	2605 (7.0)	2206 (18.3)	< 0.001	4811 (9.8)	949 (1.2)	774 (3.0)	< 0.001	1723 (1.7)
Twice	773 (2.1)	996 (8.3)		1769 (3.6)	310 (0.4)	349 (1.3)		659 (0.6)
Three times	308 (0.8)	507 (4.2)		815 (1.7)	126 (0.2)	179 (0.7)		305 (0.3)
Four times	265 (0.7)	679 (5.6)		944 (1.9)	162 (0.2)	302 (1.2)		464 (0.4)
Inflammatory bowel disease, *n* (%)								
Present	160 (0.4)	104 (0.9)	< 0.001	264 (0.5)	82 (0.1)	54 (0.2)	< 0.001	136 (0.1)
IBS, *n* (%)								
Present	1716 (4.6)	1346 (11.2)	< 0.001	3062 (6.2)	757 (1.0)	545 (2.1)	< 0.001	1302 (1.3)
IgA deficiency, *n* (%)								
Present	2 (0.0)	6 (0.0)	0.004	8 (0.0)	1 (0.0)	7 (0.0)	< 0.001	8 (0.0)
Iron, vitamin B_{12} or folate deficiency, *n* (%)								
Present	505 (1.4)	938 (7.8)	< 0.001	1443 (2.9)	235 (0.3)	394 (1.5)	< 0.001	629 (0.6)
Mouth ulcers (count, 1 year), *n* (%)								
Once	110 (0.3)	121 (1.0)	< 0.001	231 (0.5)	43 (0.1)	32 (0.1)	< 0.001	75 (0.1)
Twice	12 (0.0)	38 (0.3)		50 (0.1)	11 (0.0)	16 (0.1)		27 (0.0)
Neuropathy or ataxia, *n* (%)								
Present	84 (0.2)	55 (0.5)	< 0.001	139 (0.3)	56 (0.1)	36 (0.1)	0.003	92 (0.1)
Osteoporosis, *n* (%)								
Present	915 (2.5)	898 (7.5)	< 0.001	1813 (3.7)	367 (0.5)	305 (1.2)	< 0.001	672 (0.6)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
Systemic lupus erythematosus, *n* (%)								
Present	42 (0.1)	40 (0.3)	< 0.001	82 (0.2)	23 (0.0)	18 (0.1)	< 0.001	41 (0.0)
Type 1 diabetes, *n* (%)								
Present	99 (0.3)	141 (1.2)	< 0.001	240 (0.5)	223 (0.3)	147 (0.6)	< 0.001	370 (0.4)
Thyroid disorders, *n* (%)								
Present	2042 (5.5)	1442 (12.0)	< 0.001	3484 (7.1)	815 (1.1)	623 (2.4)	< 0.001	1438 (1.4)
Turner syndrome, *n* (%)								
Present	3 (0.0)	5 (0.0)	0.037	8 (0.0)	0 (0)	5 (0.0)	< 0.001	5 (0.0)
Weight loss, *n* (%)								
Present	500 (1.3)	672 (5.6)	< 0.001	1172 (2.4)	105 (0.1)	145 (0.6)	< 0.001	250 (0.2)
Men	***(N = 35,264)***	***(N = 6035)***		***(N = 41,299)***	***(N = 76,775)***	***(N = 12,385)***		***(N = 89,160)***
Age (years)								
Mean (SD)	47.5 (16.4)	53.9 (16.3)	< 0.001	48.4 (16.6)	46.6 (16.5)	52.4 (17.1)	< 0.001	47.4 (16.7)
Median (minimum, maximum)	47.0 (18.0, 103)	55.0 (18.0, 94.0)		48.0 (18.0, 103)	46.0 (18.0, 107)	53.0 (18.0, 98.0)		47.0 (18.0, 107)
Ethnicity, *n* (%)								
Non-white	535 (1.5)	94 (1.6)	0.022	629 (1.5)	976 (1.3)	155 (1.3)	< 0.001	1131 (1.3)
White	10,083 (28.6)	2315 (38.4)		12,398 (30.0)	8967 (11.7)	2100 (17.0)		11,067 (12.4)
Missing	24,646 (69.9)	3626 (60.1)		28,272 (68.5)	66,832 (87.0)	10,130 (81.8)		76,962 (86.3)

continued

TABLE 2 Cohort of children, women and men: characteristics (*continued*)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
Deprivation (IMD 2015 quintiles), *n* (%)								
1	2563 (7.3)	624 (10.3)	0.005	3187 (7.7)	4205 (5.5)	682 (5.5)	0.55	4887 (5.5)
2	2389 (6.8)	597 (9.9)		2986 (7.2)	3745 (4.9)	625 (5.0)		4370 (4.9)
3	2264 (6.4)	450 (7.5)		2714 (6.6)	3038 (4.0)	478 (3.9)		3516 (3.9)
4	1852 (5.3)	399 (6.6)		2251 (5.5)	2745 (3.6)	431 (3.5)		3176 (3.6)
5	1550 (4.4)	339 (5.6)		1889 (4.6)	2139 (2.8)	316 (2.6)		2455 (2.8)
Missing	24,646 (69.9)	3626 (60.1)		28,272 (68.5)	60,903 (79.3)	9853 (79.6)		70,756 (79.4)
Anaemia, *n* (%)								
Present	208 (0.6)	733 (12.1)	< 0.001	941 (2.3)	104 (0.1)	305 (2.5)	< 0.001	409 (0.5)
Cardiovascular disease, *n* (%)								
Present	2081 (5.9)	860 (14.3)	< 0.001	2941 (7.1)	822 (1.1)	321 (2.6)	< 0.001	1143 (1.3)
Chronic liver disease, *n* (%)								
Present	421 (1.2)	184 (3.0)	< 0.001	605 (1.5)	311 (0.4)	140 (1.1)	< 0.001	451 (0.5)
Down syndrome, *n* (%)								
Present	6 (0.0)	6 (0.1)	0.002	12 (0.0)	1 (0.0)	4 (0.0)	< 0.001	5 (0.0)
Epilepsy, *n* (%)								
Present	207 (0.6)	69 (1.1)	< 0.001	276 (0.7)	101 (0.1)	45 (0.4)	< 0.001	146 (0.2)
Fatigue, *n* (%)								
Present	1941 (5.5)	881 (14.6)	< 0.001	2822 (6.8)	710 (0.9)	346 (2.8)	< 0.001	1056 (1.2)

Cohort and characteristic	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
	Control	CD	*p*-value	Overall	Control	CD	*p*-value	Overall
Fatigue (count, 1 year), *n* (%)								
Once	396 (1.1)	288 (4.8)	< 0.001	684 (1.7)	113 (0.1)	87 (0.7)	< 0.001	200 (0.2)
Twice	50 (0.1)	63 (1.0)		113 (0.3)	28 (0.0)	35 (0.3)		63 (0.1)
Three times	17 (0.0)	22 (0.4)		39 (0.1)	15 (0.0)	34 (0.3)		49 (0.1)
First-degree relative with CD, *n* (%)								
Present	103 (0.3)	157 (2.6)	< 0.001	260 (0.6)	NR	NR		NR
GI symptoms, *n* (%)								
Present	7850 (22.3)	3164 (52.4)	< 0.001	11,014 (26.7)	2974 (3.9)	1154 (9.3)	< 0.001	4128 (4.6)
GI symptoms (count, 1 year), *n* (%)								
Once	1482 (4.2)	1030 (17.1)	< 0.001	2512 (6.1)	535 (0.7)	306 (2.5)	< 0.001	841 (0.9)
Twice	421 (1.2)	483 (8.0)		904 (2.2)	170 (0.2)	172 (1.4)		342 (0.4)
Three times	134 (0.4)	247 (4.1)		381 (0.9)	60 (0.1)	76 (0.6)		136 (0.2)
Four times	115 (0.3)	272 (4.5)		387 (0.9)	100 (0.1)	144 (1.2)		244 (0.3)
IBS, *n* (%)								
Present	597 (1.7)	339 (5.6)	< 0.001	936 (2.3)	288 (0.4)	142 (1.1)	< 0.001	430 (0.5)
Iron, vitamin B_{12} or folate deficiency, *n* (%)								
Present	193 (0.5)	429 (7.1)	< 0.001	622 (1.5)	104 (0.1)	163 (1.3)	< 0.001	267 (0.3)
Mouth ulcers, *n* (%)								
Present	331 (0.9)	170 (2.8)	< 0.001	501 (1.2)	142 (0.2)	76 (0.6)	< 0.001	218 (0.2)
Mouth ulcers (count, 1 year), *n* (%)								
Once	50 (0.1)	42 (0.7)	< 0.001	92 (0.2)	32 (0.0)	19 (0.2)	< 0.001	51 (0.1)
Twice	4 (0.0)	9 (0.1)		13 (0.0)	3 (0.0)	8 (0.1)		11 (0.0)

continued

TABLE 2 Cohort of children, women and men: characteristics (*continued*)

	Development data set (CPRD GOLD)				External validation data set (CPRD Aurum)			
Cohort and characteristic	**Control**	**CD**	***p*-value**	**Overall**	**Control**	**CD**	***p*-value**	**Overall**
Osteoporosis, *n* (%)								
Present	118 (0.3)	145 (2.4)	< 0.001	263 (0.6)	42 (0.1)	62 (0.5)	< 0.001	104 (0.1)
Psoriasis, *n* (%)								
Present	722 (2.0)	237 (3.9)	< 0.001	959 (2.3)	290 (0.4)	85 (0.7)	< 0.001	375 (0.4)
Type 1 diabetes, *n* (%)								
Present	119 (0.3)	126 (2.1)	< 0.001	245 (0.6)	324 (0.4)	150 (1.2)	< 0.001	474 (0.5)
Thyroid disorders, *n* (%)								
Present	389 (1.1)	287 (4.8)	< 0.001	676 (1.6)	166 (0.2)	130 (1.0)	< 0.001	296 (0.3)
Weight loss, *n* (%)								
Present	340 (1.0)	467 (7.7)	< 0.001	807 (2.0)	85 (0.1)	100 (0.8)	< 0.001	185 (0.2)

NR, not reported.

Note
p-values show the result of a Welch two-sample *t*-test for continuous variables and of a Pearson's chi-squared test with Yates' continuity correction for categorical variables.

Data on ethnicity and deprivation, through linkages with hospital records, were available for approximately one-third of the development data set and one-fifth of the validation data set. In all cohorts, of the patients with known ethnicity, 90–95% were white, and CD patients were more likely to be white than controls. People with CD in the development data set lived in more deprived areas (IMD quintiles 1 and 2) than the controls. This was not the case for CD patients in the validation data set.

All selected indicators were significantly different between cases and controls in all three cohorts of the development data set, except for Down syndrome among women. Although the prevalence of Down syndrome among women with CD was 4 in 10,000, compared with 1 in 10,000 among controls in both data sets, this difference did not reach statistical significance because of the small number of individuals with Down syndrome. In the validation data set for women, epilepsy was also more prevalent in the CD group, but this did not reach statistical significance because of small numbers. In the validation data set with children, arthritis and delayed puberty were not related to CD. In both data sets with men, all indicators were significantly more prevalent among people with CD than among controls.

The most important difference between the development and the validation data sets was that first-degree relatives with CD was not recorded in the validation data set. There are also small differences in prevalences of indicators, with most indicators being more prevalent in the development data set than in the validation data set. For instance, the most prevalent indicator was GI symptoms in all three cohorts. In the development data set, these prevalences ranged from 27% to 40%, whereas the prevalences in the validation data set ranged from 5% to 7%.

Diagnostic indicator selection

The following candidate diagnostic indicators (see *Appendix 9*, *Table 52*) could not be considered in the model because there were no observations with the relevant codes: hyposplenism or functional asplenia, raised liver enzymes, multiple sclerosis, pancreatitis, pulmonary haemosiderosis, subfertility and recurrent pregnancy loss among children; delayed puberty and pulmonary haemosiderosis in women; amenorrhoea and Turner syndrome among men. There were no observations of Williams–Beuren syndrome or dental enamel defects in any of the samples.

Table S8 (see *Report Supplementary Material 1*) presents the proportion of bootstrap samples that included each indicator and the median beta coefficient across all bootstrap samples.

The following indicators were dropped from the model because of an apparent inverse relationship with CD: amenorrhoea, arthritis, irritability, mood disorders, multiple sclerosis, subfertility and type 2 diabetes for women; and type 2 diabetes for men. Attention deficit hyperactivity disorder, headaches, migraines, hyposplenism or functional asplenia, IgA nephropathy, irritability, pancreatitis, type 2 diabetes and multiple sclerosis were not selected as important indicators in any of the models.

Model specification

The model intercepts and coefficients of the final prediction models are presented in *Table 3*. For children, having type 1 diabetes, Turner syndrome, IgA deficiency or a first-degree relative with CD were estimated to be the strongest diagnostic indicators (i.e. had the highest estimated coefficients). For women and men, the strongest predictors were having a first-degree relative with CD, and anaemia. All three models included first-degree relatives (with CD); anaemia; type 1 diabetes; iron, vitamin B_{12} or folate deficiency; thyroid disorders; weight loss; Down syndrome; GI symptoms; fatigue; IBS; and age. Epilepsy, cardiovascular disease, chronic liver disease, mouth ulcers and osteoporosis were estimated to be important indicators for adults, but not for children; arthritis, failure to thrive, mood disorders and delayed puberty were estimated to be predictive of CD in children, but not in adults. Fractures, inflammatory bowel disorder, systemic lupus erythematosus, and neuropathy or ataxia were selected indicators for women only. *Appendix 11*, *Tables 53–55*, report the effect of the applied shrinkage, showing coefficients with and coefficients without shrinkage, and report the adjusted and unadjusted odds ratios for each indicator for children, women and men, respectively.

TABLE 3 Model specification

Selected diagnostic indicator	Children			Women			Men		
	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)
(Intercept)	−5.119		−5.127 (−5.146 to −5.108)	−5.063		−5.062 (−5.080 to −5.042)	−5.478		−5.488 (−5.526 to −5.460)
Age	0.011	19	0.011 (0.007–0.014)	−0.006	25	−0.006 (−0.006 to −0.005)	0.01	20	0.011 (0.010–0.011)
Anaemia	2.645	5	2.618 (2.522–2.751)	1.63	2	1.635 (1.605–1.661)	2.685	1	2.689 (2.632–2.753)
Arthritis	1.318	12	1.371 (0.949–1.738)	NS	NS	NS	NS	NS	NS
Cardiovascular disease	NS	NS	NS	0.196	20	0.190 (0.139–0.222)	0.253	18	0.243 (0.214–0.282)
Chronic liver disease	NS	NS	NS	0.326	16	0.324 (0.245–0.383)	0.321	16	0.321 (0.236–0.396)
Delayed puberty	1.995	10	1.997 (1.537–2.577)	NS	NS	NS	NS	NS	NS
Down syndrome	2.429	6	2.428 (2.096–2.763)	1.163	5	1.269 (1.161–1.358)	1.293	7	1.344 (0.856–1.813)
Epilepsy	NS	NS	NS	0.258	17	0.252 (0.232–0.268)	0.259	17	0.290 (0.147–0.384)
Failure to thrive	1.382	11	1.398 (1.215–1.540)	NS	NS	NS	NS	NS	NS
Fatigue	0.613	16	0.605 (0.500–0.698)	0.153	22	0.151 (0.127–0.178)	0.185	19	0.186 (0.136–0.233)
Fatigue (count 1 year)	1.111	14	1.090 (0.967–1.233)	0.545	14	0.544 (0.518–0.571)	0.663	12	0.652 (0.592–0.714)
First-degree relative with CD	3.1	4	3.109 (3.037–3.172)	2.459	1	2.449 (2.378–2.517)	2.347	2	2.362 (2.282–2.461)
Fractures (count 1 year)	NS	NS	NS	0.196	19	0.203 (0.167–0.241)	NS	NS	NS
GI symptoms	0.582	17	0.584 (0.550–0.613)	0.249	18	0.251 (0.173–0.360)	0.448	13	0.442 (0.414–0.472)
GI symptoms (count 1 year)	0.794	15	0.792 (0.775–0.817)	0.604	12	0.604 (0.594–0.615)	0.787	10	0.789 (0.772–0.807)
IgA deficiency	3.21	3	3.185 (2.287–3.563)	1.127	6	1.170 (0.765–1.596)	NS	NS	NS
Inflammatory bowel disease	NS	NS	NS	0.138	23	0.112 (0.000–0.227)	NS	NS	NS

Selected diagnostic indicator	Children			Women			Men		
	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)	Coefficient	Rank[a]	200 bootstrapped samples, median (IQR)
Iron, vitamin B_{12} or folate deficiency	2.016	9	2.013 (1.704–2.363)	1.323	3	1.383 (0.554–2.113)	1.81	3	1.828 (1.754–1.917)
IBS	1.127	13	1.135 (0.934–1.377)	0.478	15	0.474 (0.450–0.505)	0.709	11	0.714 (0.651–0.776)
Mood disorders	0.363	18	0.343 (0.250–0.448)	NS	NS	NS	NS	NS	NS
Mouth ulcers	NS	NS	NS	NS	NS	NS	0.412	14	0.401 (0.305–0.514)
Mouth ulcers (count 1 year)	NS	NS	NS	0.857	10	0.841 (0.767–0.907)	0.934	8	0.919 (0.849–0.994)
Neuropathy or ataxia	NS	NS	NS	0.179	21	0.178 (0.074–0.311)	–	–	–
Osteoporosis	NS	NS	NS	1.028	8	1.040 (1.000–1.077)	1.554	5	1.549 (1.433–1.673)
Psoriasis	NS	NS	NS	0.048	24	0.047 (0.000–0.097)	0.335	15	0.339 (0.265–0.401)
Sex (male)	−0.477	20	−0.472 (−0.502 to −0.447)	NS	NS	NS	NS	NS	NS
Systemic lupus erythematosus	NS	NS	NS	0.699	11	0.698 (0.532–0.856)	NS	NS	NS
Thyroid disorders	2.144	8	2.185 (2.000–2.395)	0.599	13	0.598 (0.563–0.629)	0.91	9	0.913 (0.753–1.074)
Turner syndrome	3.949	2	3.908 (3.715–4.084)	1.08	7	1.057 (0.422–1.681)	NS	NS	NS
Type 1 diabetes	4.153	1	4.182 (4.062–4.278)	1.277	4	1.337 (1.293–1.375)	1.746	4	1.749 (1.650–1.868)
Weight loss	2.316	7	2.302 (2.142–2.485)	0.91	9	0.895 (0.848–0.950)	1.49	6	1.489 (1.431–1.552)

NS, not selected.
a Highest to lowest coefficient.

Model performance

The amount of variability explained (R^2), the overall model fit (Brier score), discrimination (*c*-statistic), and calibration measures (intercept and slope of calibration curve) are shown in *Table 4*.

The development model for children shows the best overall model fit and ability to discriminate between those with and those without CD, compared with the models for men and women. The calibration slope is < 1 for all three models, meaning that all three models overestimate the risk of CD, on average (see *Appendix 12*, *Figure 55*). For instance, the model for children estimates a 40% chance of CD, compared with a prevalence in the data set of 20%. At higher risks, the model performs better. The estimated model performance appears to be stable, as the internal model performance in 200 bootstrapped samples was similar, with narrow CIs (see *Table 4*).

TABLE 4 Model performance

Data	Apparent model performance: original data set (CPRD GOLD)	Internally validated model performance: 200 bootstrapped samples of original data, median (IQR)	Externally validated model performance: independent data set (CPRD Aurum)
Children			
R^2	0.407	0.408 (0.401–0.413)	0.065
Brier score	0.167	0.167 (0.165–0.169)	Without FDR: 0.190 With FDR: 0.156
c-statistic	0.821	0.821 (0.818–0.824)	0.600
Calibration intercept[a]	0.147	0.161 (0.134–0.181)	Without FDR: 0.433 With FDR: –2.676
Calibration slope[a]	0.964	0.986 (0.959–1.014)	0.655
Women			
R^2	0.237	0.248 (0.242–0.254)	0.032
Brier score	0.227	0.225 (0.223–0.227)	Without FDR: 0.245 With FDR: 0.217
c-statistic	0.756	0.764 (0.761–0.767)	0.551
Calibration intercept[a]	–0.161	–0.153 (–0.169 to –0.143)	Without FDR: 0.433 –2.676
Calibration slope[a]	0.822	0.836 (0.817–0.855)	0.655
Men			
R^2	0.286	0.284 (0.278–0.291)	0.056
Brier score	0.122	0.124 (0.122–0.126)	Without FDR: 0.134 With FDR: 0.118
c-statistic	0.798	0.796 (0.793;0.801)	0.619
Calibration intercept[a]	–0.505	–0.515 (–0.534 to–0.497)	Without FDR: 0.112 With FDR: –2.250
Calibration slope[a]	0.934	0.840 (0.817–0.867)	0.668

FDR, first-degree relative.
a Calibration statistics were estimated using an inflated control group to adjust for sampling frequency.

External validation

The prevalence of each predictor was generally lower in the external validation data set. The models performed less well in the validation data set. The amount of variability explained by the model dropped to < 7% in all models. The *c*-statistics were > 0.5, suggesting that the models discriminated better than chance. Calibration intercepts were further away from 0 and calibration slopes further away from 1 than for the apparent model performance. The R^2, *c*-statistic and calibration slope were not different for people with or people without a first-degree relative with CD.

Clinical usefulness

Table 5 shows the sensitivity and specificity of the prediction model at several thresholds to achieve a 1.5%, 2%, 5%, 10% or 20% PPV of the prediction model. This can also be considered as the pre-test probability for serological testing, the next stop on the diagnostic pathway. The lowest pre-test probability (1%) is the estimated prevalence of CD in the general population, so this strategy is the same as testing everyone. By definition, this strategy is 100% sensitive and 0% specific because a test is offered to anyone regardless of their diagnostic indicators. Currently in the UK, only one in three people with CD is believed to be diagnosed, so a prediction rule that picks up more than one in three (i.e. sensitivity of > 33%) might already improve case-finding. As can be see in *Table 5*, this can be achieved at a pre-test probability of > 20% for children, > 5% for women and > 10% for men. *Table 6* shows examples of the combination of predictors among patients at these model thresholds.

TABLE 5 Clinical usefulness in development data

Population	PPV (%)	Threshold	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity (%)	Specificity (%)	NPV (%)	CD patients missed (%)
Children	1	0	100	9900	0	0	100.0	0.0	NA	0
	1.5	0.0038	88	5776	12	4124	88.2	41.7	99.7	11.8
	2	0.0042	81	3865	19	6035	80.7	61.0	99.7	19.3
	5	0.0077	67	1271	33	8629	66.7	87.2	99.6	33.3
	10	0.0170	53	478	47	9422	53.3	95.2	99.5	46.7
	20	0.0800	33	129	67	9771	33.1	98.7	99.3	66.9
Women	1	0	100	9900	0	0	100.0	0.0	NA	0
	1.5	0.0053	84	5468	16	4432	84.1	44.8	99.6	15.9
	2	0.0062	76	3687	24	6213	75.8	62.8	99.6	24.2
	5	0.0233	39	731	61	9169	38.7	92.6	99.3	61.3
	10	0.1070	11	96	89	9804	10.7	99.0	99.1	89.3
	20	0.7550	0	1	100	9899	0.2	100.0	99.0	99.8
Men	1	0	100	9900	0	0	100.0	0.0	NA	0
	1.5	0.007	87	5634	13	4266	87.0	43.1	99.7	13
	2	0.008	79	3858	21	6042	79.0	61.0	99.7	21
	5	0.0185	58	1095	42	8805	57.9	88.9	99.5	42.1
	10	0.0610	32	290	68	9610	32.2	97.1	99.3	67.8
	20	0.2820	11	43	89	9857	10.7	99.6	99.1	89.3

FN, false negative; FP, false positive; NA, not applicable; NPV, negative predictive value; TN, true negative; TP, true positive.

Note
In a population of 10,000 people.

TABLE 6 Examples of the combination of predictors among patients at several model thresholds

Risk (%)	Children	Women	Men
> 1.5	All female children	• CVD • Neuropathy or ataxia • Fatigue[a] • GI symptoms[a]	Fatigue[a]
> 2	• Mood disorders • GI symptoms[a] • Fatigue[a]	• GI symptoms[a] and psoriasis • CVD, GI symptoms[a] • Chronic liver disease • IBS • Thyroid disease	• CVD • IBS • GI symptoms[a] • Mouth ulcers[a] • Epilepsy
> 5	• Fatigue within previous year • IBS • Arthritis • Failure to thrive	• Fatigue[a], GI symptoms[a] and once last year, and IBS • Anaemia • Fatigue[a] and thyroid disorder • First-degree relative with CD	• GI symptoms,[a] and chronic liver disease or epilepsy • Down syndrome • Weight loss
> 10	• GI symptoms[a] (and once in previous year) • Failure to thrive and GI symptoms[a] • Iron/folate/vitamin B_{12} deficiency • Thyroid disorders • Down syndrome • Anaemia	• Anaemia, GI symptoms,[a] iron/folate/B_{12} deficiency • GI symptoms[a] (and four times in previous year), IBS • Chronic liver disease, fatigue[a] (and once in previous year), GI symptoms[a] (and three times in previous year) • GI symptoms,[a] IBS, osteoporosis	• GI symptoms[a] (and twice in previous year) • Type 1 diabetes, fatigue,[a] GI symptoms[a] • Fatigue, FDR with CD • GI symptoms,[a] osteoporosis • Anaemia
> 20	• FDR with CD • IgA deficiency • Turner syndrome • Type 1 diabetes	• Anaemia, fatigue,[a] GI symptoms[a] (and four times in previous year), iron/vitamin B_{12}/folate deficiency, thyroid disorder • Anaemia, fatigue[a] (and three times in previous year), GI symptoms[a] (and twice in previous year), inflammatory bowel disease, osteoporosis, thyroid disorder • Anaemia, CVD, GI symptoms[a] (and four times in previous year), iron/vitamin B_{12}/folate deficiency, weight loss	• Fatigue,[a] GI symptoms,[a] iron/vitamin B_{12}/folate deficiency • Fatigue[a] (and once in previous year), GI symptoms,[a] thyroid disorders • GI symptoms[a] (and four times in previous year), IBS • CVD, GI symptoms[a] (and once in previous year), mouth ulcers[a] (and twice in previous year)

CVD, cardiovascular disease; FDR, first-degree relative.
a Symptoms that occurred within the previous 10 years.

The ROC curves in *Figure 2* show that the model performs less well with the external data and the ROC curves are closer to the chance line, corresponding to a lower *c*-statistic. When applying the prediction rule in the external validation data sets, at the 20% threshold for children, 95% of people with CD are missed; at the 5% threshold for women, 86% of people with CD are missed; and at the 10% threshold for men, 94% of people with CD are missed. However, lower thresholds still appear to be able to pick up more than the one in three people with CD, which is how many people with CD are thought to currently have a CD diagnosis (see *Appendix 13*, *Table 56*).

Sensitivity analysis on coeliac disease patients diagnosed after 1997

The vast majority of patients in the CPRD GOLD data set were diagnosed after 1997, so limiting the analysis to these patients did not make a big impact on sample size. For this sensitivity analysis, 495 (3%) children, 2039 (4%) women and 1591 (4%) men were removed from the development data sets. Although there were minor changes in variable selection and model performance measures, the new models did not perform substantially better or worse than the original models.

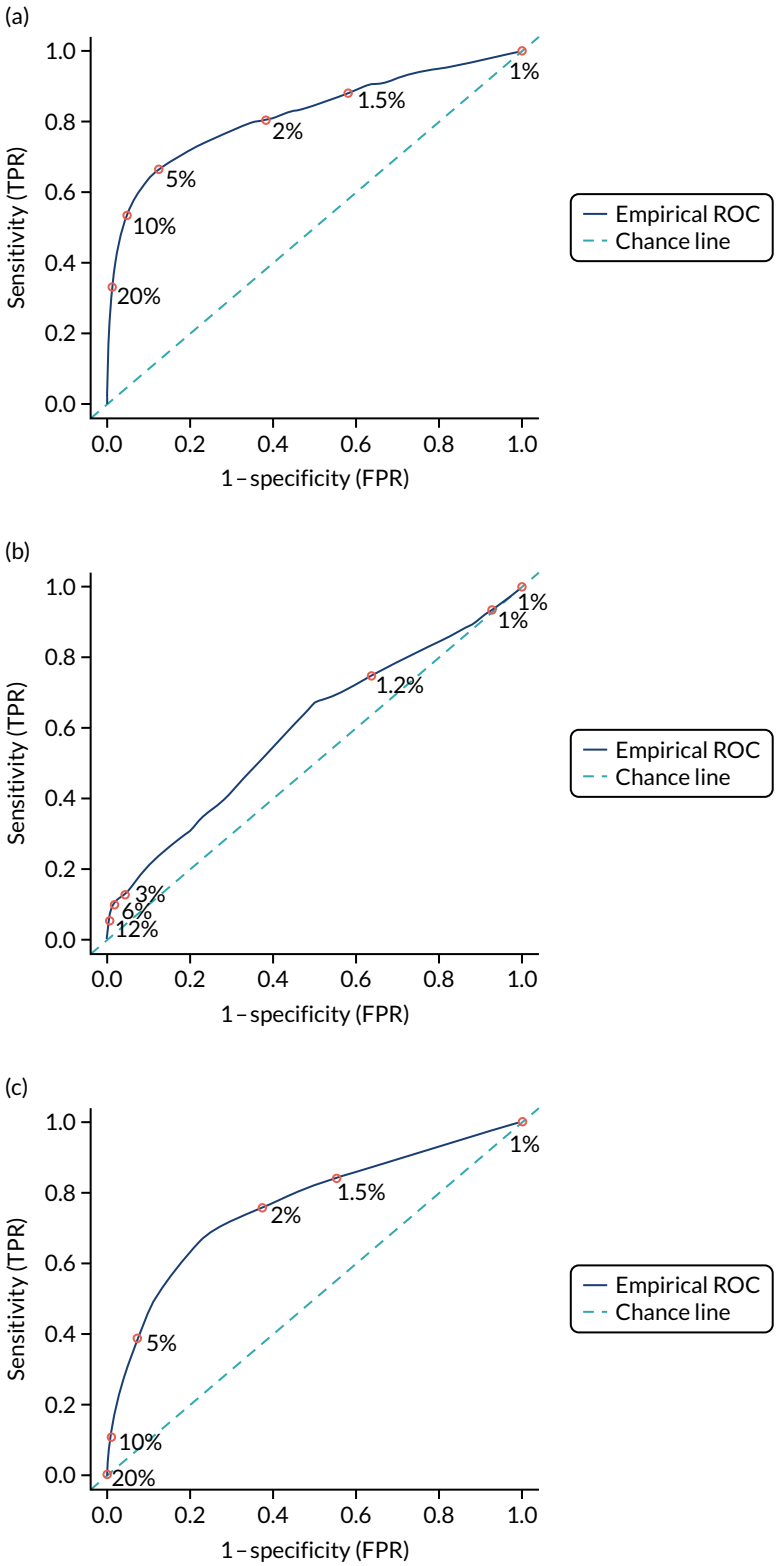

FIGURE 2 The ROC curves model development. (a) Children: development sample; (b) children: external validation; (c) women: development sample; (d) women: external validation; (e) men: development sample; and (f) men: external validation. Thresholds are shown that result in a 1%, 1.5%, 2%, 5%, 10% and 20% PPV. The same thresholds are applied on the external data. FPR, false-positive rate; TPR, true-positive rate. (*continued*)

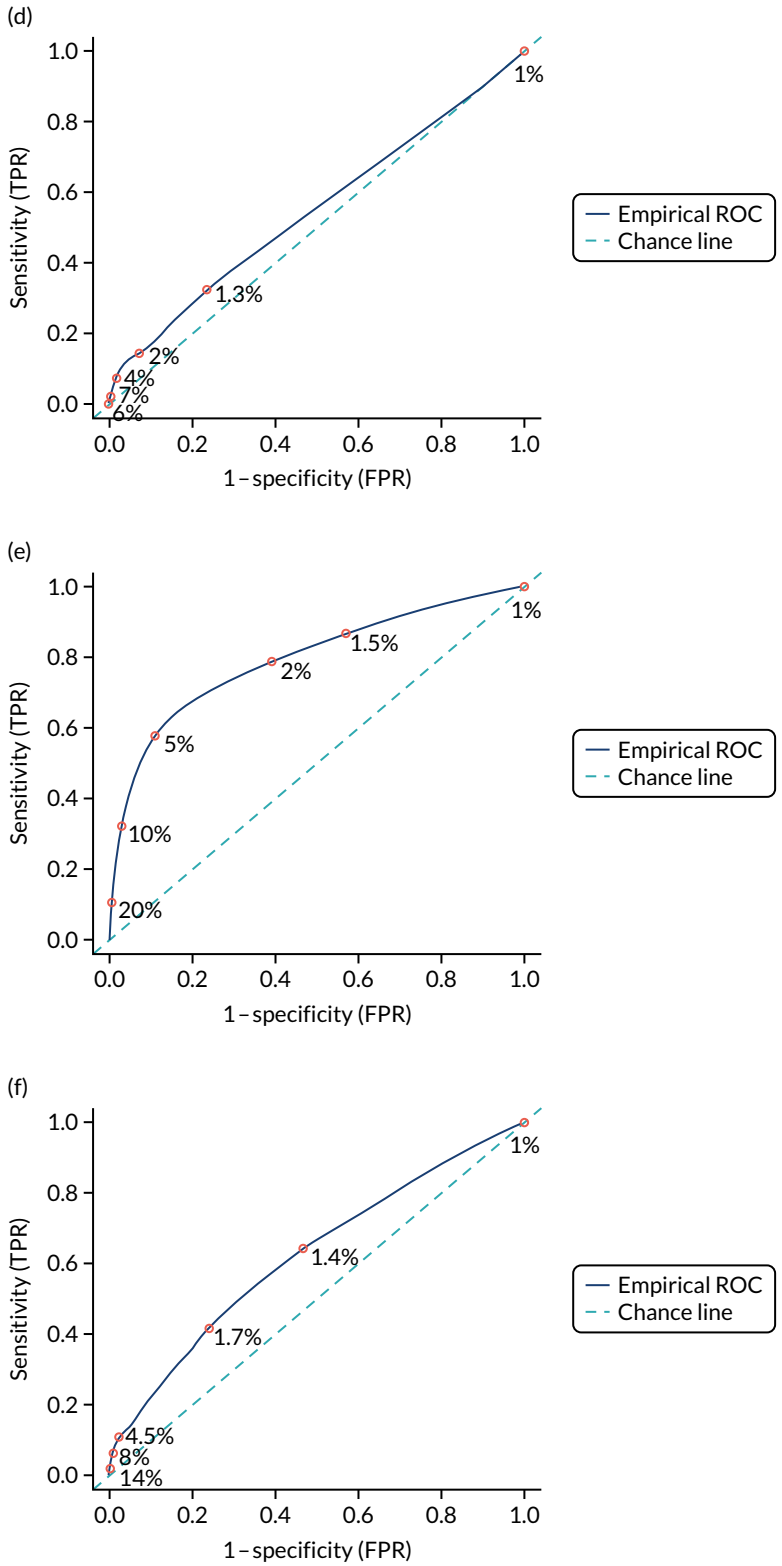

FIGURE 2 The ROC curves model development. (a) Children: development sample; (b) children: external validation; (c) women: development sample; (d) women: external validation; (e) men: development sample; and (f) men: external validation. Thresholds are shown that result in a 1%, 1.5%, 2%, 5%, 10% and 20% PPV. The same thresholds are applied on the external data. FPR, false-positive rate; TPR, true-positive rate.

Children

The same predictors and two additional predictors, amenorrhoea and mouth ulcers (as count, 2 years prior to CD diagnosis), were included in the model. However, this did not seem to improve model performance: all performance measures were similar between the new and the original models ($R^2 = 0.415$, Brier score = 0.166, *c*-statistic = 0.827, calibration intercept = 0.113 and calibration slope = 1.011).

Women

In the new model, inflammatory bowel disease, psoriasis, and neuropathy or ataxia were not included, following the same model selection criteria as for the original model. The new model performed similarly to the original model ($R^2 = 0.246$, Brier score = 0.222, *c*-statistic = 0.763, calibration intercept = −0.162 and calibration slope = 0.814).

Men

The results were similar for men. With the same model selection procedure, epilepsy was not included in the new model, whereas abnormal liver function was included (which was not included in the original model). However, model performance was similar to that of the original model ($R^2 = 0.282$, Brier score = 0.124, *c*-statistic = 0.797, calibration intercept = −0.543 and calibration slope = 0.829).

Sensitivity analysis including ethnicity and deprivation as predictions

Information on ethnicity and 2015 IMD[67] was available for only one-third of the CPRD GOLD cohort. The linked data set consisted of 4254 controls and 1303 CD patients for children; 13,093 controls and 4824 CD patients for women; and 10,618 controls and 2409 CD patients for men. CD prevalence was higher in the linked data sets (at 23.4%, 26.9% and 18.5% for children, women and men, respectively) than in the original data sets (20%, 24.5%, and 14.6% for children, women and men, respectively). Although ethnicity and 2015 IMD[67] quintiles were significantly associated with CD in all three samples, the updated model did not perform substantially better (see *Appendix 14*, *Table 57*).

The Avon Longitudinal Study of Parents and Children analysis

Table 7 describes the prevalence of candidate predictors among children with (*n* = 46) and children without CD (*n* = 5071). A significantly higher proportion of children with CD were female (67% female vs. 33% male); the mean age of children with and children without CD was similar (7.5 years). There were no significant differences in the prevalence of any of the other candidate predictors between children with and children without CD. The most prevalent predictors were male sex (52%), fatigue (23%), mood disorder (12%) and mouth ulcers (10%). With the exception of age, candidate predictors were missing for between 0.2% and 60% of children.

TABLE 7 Cohort of children: prevalence of predictors

Predictor	Children without CD (*N* = 5071)	Children with CD (*N* = 46)	*p*-value[a]
Type 1 diabetes, *n* (%)			
Absent	2665 (52.6)	30 (65.2)	0.119
Present	< 5 (< 0.01)	< 5 (< 10.9)[b]	
Missing	2404 (47.4)	16 (34.8)	
Anaemia, *n* (%)			
Absent	4881 (96.3)	43 (93.5)	0.326
Present	150 (3.0)	< 5 (< 10.9)[b]	
Missing	40 (0.8)	< 5 (< 10.9)[b]	

continued

TABLE 7 Cohort of children: prevalence of predictors (*continued*)

Predictor	Children without CD (*N* = 5071)	Children with CD (*N* = 46)	*p*-value[a]
Thyroid disorder, *n* (%)			
Absent	3297 (65.0)	30 (65.2)	1.000
Present	37 (0.7)	< 5 (< 10.9)[b]	
Missing	1737 (34.3)	16 (34.8)	
GI symptom count, *n* (%)			
0	3840 (75.7)	40 (87.0)	0.225
1	207 (4.1)	< 5 (< 10.9)[b]	
2–4	79 (1.6)	< 5 (< 10.9)[b]	
Missing	945 (18.6)	< 5 (< 10.9)[b]	
Sex, *n* (%)			
Female	2444 (48.2)	31 (67.4)	0.027
Male	2618 (51.6)	15 (32.6)	
Missing	9 (0.2)	< 5 (< 10.9)[b]	
Fatigue, *n* (%)			
Absent	2767 (54.6)	25 (54.3)	0.960
Present	1165 (23.0)	10 (21.7)	
Missing	1139 (22.5)	11 (23.9)	
Mouth ulcers, *n* (%)			
Absent	1554 (30.6)	16 (34.8)	0.857
Present	497 (9.8)	< 5 (< 10.9)[b]	
Missing	3020 (59.6)	26 (56.5)	
GI symptoms, *n* (%)			
Absent	3840 (75.7)	40 (87.0)	0.235
Present	306 (6.0)	< 5 (< 10.9)[b]	
Missing	925 (18.2)	< 5 (< 10.9)[b]	
Mood disorders, *n* (%)			
Absent	3573 (70.5)	38 (82.6)	0.229
Present	608 (12.0)	< 5 (< 10.9)[b]	
Missing	890 (17.6)	5 (10.9)	
Age (years), mean (SD)	7.49 (0.19)	7.45 (0.12)	0.030

a *p*-values show the result of a Welch two-sample *t*-test for continuous variables and Fisher's exact test for categorical variables.
b This may include zero.

Among children for whom complete data for the outcome and each candidate predictor were available, univariable associations indicated that males were less likely to have CD than females (coefficient −0.78, 95% CI −1.39 to −0.17; see *Appendix 15*, *Table 58*) (*Figure 3*). Children with type 1 diabetes, anaemia, a thyroid disorder or two to four GI symptoms were more likely to have CD; however, the 95% CIs contain zero. None of the remaining candidate predictors showed evidence of association with an increased likelihood of CD.

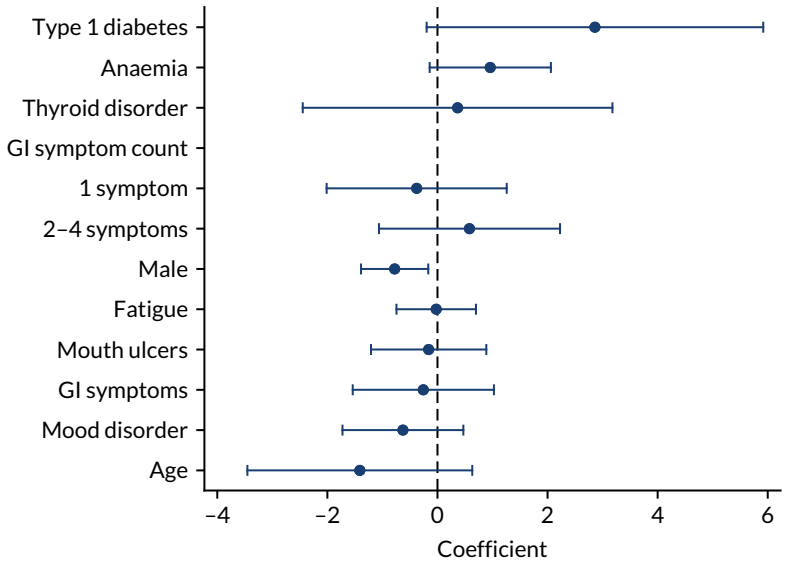

FIGURE 3 Coefficients and 95% CIs from complete-case univariable analysis of candidate predictors and CD.

Male sex was the only predictor that showed evidence of an association with CD in the ALSPAC data set, with male children less likely than female children to be diagnosed with CD. This finding is consistent with the association between male sex and CD in the CPRD data. For the predictors age, mood disorder, fatigue, mouth ulcers, GI symptoms and GI symptom count of 1, the direction of effects estimated in the ALSPAC cohort contradicts the associations identified in the CPRD data; therefore, inclusion in the model is likely to result in inaccurate risk predictions. Low counts of children with type 1 diabetes and thyroid disorder precluded multiple imputation of these predictors and, because of the large number of missing data (34% and 47%, respectively), inclusion in the model would almost halve the sample size. A prediction model consisting of the remaining predictors (anaemia, two to four GI symptoms and male sex) would not be clinically useful; therefore, the decision was taken not to fit a prediction model in this data set.

Chapter 5 Accuracy of diagnostic tests for coeliac disease

We conducted a systematic review of the accuracy of serological tests for CD. The review was registered with the international prospective register of systematic reviews (PROSPERO): registration number CRD42019115506. The review followed the recommendations from the Centre for Reviews and Dissemination[22] and the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0*,[23] and is reported according to the PRISMA-DTA statement.[24]

Systematic review methods

Eligibility criteria

Inclusion criteria were defined during protocol development and piloted on a subset of 500 articles during title and abstract screening to ensure that they could be applied objectively. We included studies that met the following criteria.

Study design

Diagnostic cohort studies (also known as 'one-gate design') were included. Diagnostic case–control studies (also known as 'two-gate' designs) that enrolled a group of people with known CD and a group without CD were excluded, as this type of design has been associated with inflated estimates of accuracy. We anticipated a substantial evidence base from cohort studies and so restricted to this more methodologically robust design.[68]

Participants

People presenting with symptoms of CD (e.g. diarrhoea, abdominal pain, fatigue) were included. After piloting the inclusion criteria, we decided to exclude studies conducted with healthy individuals (i.e. screening) or those restricted to single risk groups (e.g. people with diabetes) to ensure that the review was conducted in a clinically relevant population that would be eligible to be tested for CD.

Index test

Any of the following serological tests for CD were eligible: IgA tTG, IgG tTG, IgA EMA, IgG EMA, IgA DGP, IgG DGP and IgA actin antibodies. Combined serological tests, such as IgA/IgG tTG (which detect the presence of IgA tTG or IgG tTG in a serum sample) or IgA tTG followed by IgA EMA, were also eligible for inclusion. GAs were not considered in this review, as they are not recommended for use in the diagnosis of CD by NICE as their accuracy has been shown to be poor.[9] Point-of-care or rapid serological tests were excluded as a systematic review of their accuracy was published in 2019.[69]

Reference standard

Studies had to use duodenal biopsy to confirm the diagnosis of CD; at least some seronegative patients had to have received biopsy for the study to be included. Studies in which serology formed part of the reference standard were excluded as this could lead to overestimation of test accuracy.

Search strategy

The following databases were searched from January 1990 to August 2020 for published studies and relevant reviews:

- MEDLINE
- Embase
- Cochrane Library
- Web of Science
- Kleijnen Systematic Reviews (KSR) Evidence.

To identify completed and ongoing trials, we searched the following trial registries from January 1990 to August 2020:

- WHO ICTRP
- NIH Clinical Trials database.

Internet searches were carried out using terms such as 'celiac', 'coeliac' and 'serological tests'. The reference lists of relevant systematic reviews identified during the literature search were used as sources of potentially relevant studies.

No language or publication restrictions were applied. Date restrictions were applied to limit searches to 1990 onwards, as serological tests for CD first became available in 1990.[70]

We combined terms for 'antibodies' with terms for 'coeliac disease'. Search strategies were adapted for each database searched. Full details of the search strategies are available in *Appendix 16*. Results of the searches were downloaded and saved to an EndNote X9 library.

Study selection

Titles and abstracts were uploaded to the Rayyan QCRI (Doha, Qatar; https://rayyan.qcri.org/) systematic review software platform[71] and screened independently by two reviewers. Any discrepancies were discussed; where disagreement remained, articles were considered to be potentially relevant. Articles considered potentially relevant were obtained as full-text articles and assessed by one reviewer and checked by a second reviewer against the review inclusion criteria using a Microsoft Access form designed specifically for this review. Any discrepancies between reviewers were resolved through discussion or referral to a third reviewer.

Data collection process

Standardised data extraction forms were developed using Microsoft Access. These were piloted on a small sample of papers and adapted as necessary before use. Data extraction was performed by one reviewer and checked by a second. Disagreements were resolved through discussion or referral to a third reviewer when necessary.

We extracted data on the following from each included study:

- participant characteristics – adults/children, reason for biopsy, number of participants
- serological tests – test(s) evaluated, threshold(s) for positivity
- biopsy procedures – definition of CD (biopsy threshold), proportion biopsied.

Results data were extracted as 2 × 2 tables of test results (numbers of true positives, false negatives, false positives and true negatives) for each index test against the biopsy reference standard. When reported, 2 × 2 tables for testing strategies involving combinations of serological tests were also extracted. When 2 × 2 data were reported at multiple thresholds within a study, data relating to the cut-off point prespecified by the manufacturer or author were extracted. Two-by-two data were extracted at a biopsy cut-off point of Marsh grade 3a, if available; otherwise, any reported biopsy threshold was accepted.

Risk of bias

Studies were assessed for methodological quality using the QUADAS-2 tool. This assesses the risk of bias and concerns regarding applicability across the following four domains: patient selection, index test, reference standard, and flow and timing. For this review, we omitted the assessment of applicability as the research question was defined such that any study meeting the inclusion criteria was applicable to the research question. We tailored the signalling questions to our review; the exact signalling questions used are reported in table S9 (see *Report Supplementary Material 1*).

For comparative accuracy studies, we added additional signalling questions based on a draft version of the quality assessment of diagnostic accuracy studies–comparative (QUADAS-C) tool,[72] which was under development at the time of our review, to assess the comparative nature of the studies. These are also summarised in table S9 (see *Report Supplementary Material 1*).

Each study was judged as having a 'high', 'low' or 'unclear' risk of bias in each risk-of-bias domain. If at least one of the domains was rated as having a 'high' risk of bias, the study was considered as being at high risk of bias; if all domains were judged as having a 'low' risk of bias, the study was considered as being at low risk of bias; otherwise, the study was considered as having an 'unclear' risk of bias.

When a study reported accuracy data for two or more tests, the 'index test' and 'flow and timing' domains were assessed separately for each. When a study reported accuracy data for adults and children separately, all domains were assessed separately for each patient group.

Synthesis of results

We grouped studies according to age group [adults aged > 16 years, children aged ≤ 16 years, mixed (adults and children) and age unspecified] and stratified all analyses by age group and serological test, or test combination. Meta-analyses were performed in Stata® version 16.0 (StataCorp LP, College Station, TX, USA) using the metandi command.

Primary analyses

For data sets that included at least four studies, a bivariate random-effects meta-analysis of sensitivity and specificity was performed,[29] assuming binomial likelihoods for the numbers of true-positive and true-negative test results.[30] When there were fewer than four studies in a data set, univariate fixed-effect meta-analyses of sensitivity and specificity were performed. When only a single study was available, the sensitivity and specificity reported in that study are presented.

When the extracted data on a test relate to a range of thresholds, we report results from two separate meta-analyses. First, we fitted the bivariate model to studies reporting at the most commonly reported threshold only. From these models, we report summary estimates of sensitivity and specificity at that threshold. Second, we fitted the bivariate model to the full data set. From these models, we present the SROC curve, which represents the trade-off between sensitivity and specificity across thresholds.

The sensitivity and specificity reported in each study were plotted in ROC space, with colour-coding allowing comparisons to be made between different thresholds. Summary estimates of sensitivity and specificity with 95% CIs at the most commonly reported threshold and SROC curves across all reported thresholds are presented.

Summary PPVs were calculated from estimates of sensitivity and specificity, for a hypothetical prevalence of 1%, the estimated prevalence of CD in the UK population. We then used a hypothetical population of 10,000 people tested for CD, for a pre-test probability of 1%, to produce a test consequence graphic based on natural frequencies.[73] Values were estimated based on summary sensitivity and specificity from the meta-analyses restricted to the most commonly reported threshold for the most commonly evaluated tests.

Direct comparisons and test combinations

To investigate direct comparisons between tests, we performed additional analyses restricted to studies that reported accuracy estimates for multiple tests based on the same participants (comparative accuracy studies). These studies used the design outlined in *Figure 4*.

As all patients undergo both index tests and the reference standard, these studies provide more reliable estimates of the comparative accuracy of different tests.[74] For the two most commonly assessed tests, IgA tTG and IgA EMA, we estimated the relative sensitivity and specificity within each

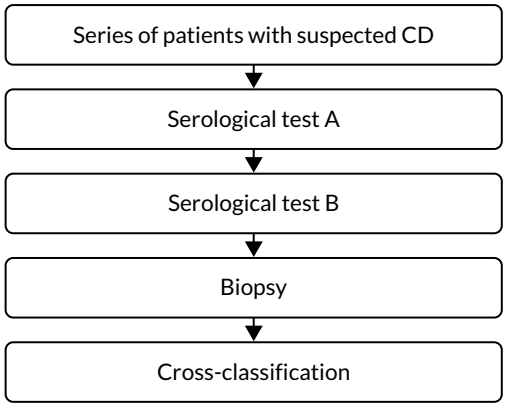

FIGURE 4 Comparative accuracy study design.

study, which are measures of the comparative accuracy of the two tests. Relative sensitivity is the ratio of two sensitivities; for example, if relative sensitivity is 1, then the sensitivity of the two tests is the same (similarly for specificity). We report the observed range of these measures across the set of studies that evaluated both of these tests in the same group of patients.

A subset of these studies also reported accuracy data for the combined accuracy of IgA tTG and IgA EMA. These provided estimates of the accuracy of considering an individual to be positive for CD if 'both tests were positive' (and negative otherwise) or of considering an individual to be positive for CD if 'either test was positive' (and negative only if both tests were negative). We tabulated estimates of sensitivity and specificity of these testing strategies, but did not pool across these studies using meta-analysis because of variation in the diagnostic thresholds used for each test.

To allow comparisons across the testing strategies that were under consideration for inclusion in the economic model (see *Chapter 8*), we performed additional analyses of the accuracy of IgA tTG in isolation and of IgA EMA in isolation, based on this same subset of comparative accuracy studies. This allowed us to make direct comparisons between the accuracy of singular tests and that of combined testing strategies. We then restricted to the most commonly reported threshold. These estimates of accuracy were selected for inclusion in the economic model (see *Chapter 8*).

Sensitivity analyses

We used sensitivity analyses to investigate whether or not estimates of accuracy varied according to study quality, patient spectrum and potential for partial verification bias. We restricted analyses to the following subsets of studies to investigate the impact of these variables:

- studies judged to be at low risk of bias overall based on the QUADAS-2
- studies that included only symptomatic patients
- studies in which all patients received a biopsy to confirm whether or not they had CD.

Deviations from the protocol

- In the protocol, we described our target population as 'adults or children at risk of CD'. After piloting the inclusion criteria at title and abstract screening, we chose to exclude studies in healthy populations (i.e. screening) or single-risk groups only, as described in *Eligibility criteria*.
- We described the intervention as 'any serological test for CD', including *HLA-DQ* typing. We decided not to include GAs as they are not recommended for use in the diagnosis of CD by NICE.[9] We did not include *HLA-DQ* typing in this chapter, as this is covered in a separate review (see *Chapter 6*). We did not include point-of-care or rapid serological tests as a systematic review of their accuracy was published in 2019.[69]

- We described our comparator as 'any reported reference standard'. After piloting the exclusion criteria at title and abstract screening, we decided to exclude studies in which serology formed part or all of the reference standard, as this would lead to overinflation of test accuracy estimates.

In the strategy for data synthesis, we stated, 'If a test is reported at a single threshold for test positivity across studies, summary operating points will be used to measure the test's accuracy. If a test is reported at differing thresholds across studies, SROC curves showing the trade-off between sensitivity and specificity at the various thresholds will be produced'.[75] In the review, we produced both summaries of the evidence for completeness: a SROC curve across all reported thresholds and summary sensitivity/specificity at the most commonly reported threshold.

Results of the assessment of diagnostic accuracy of serological tests

The electronic search identified 15,170 articles. After removing duplicates, 7956 unique reports remained. Following title and abstract screening of these 7956 reports, 398 reports were considered potentially relevant and full-text reports were requested (see *Appendix 17*, *Figure 56*). We were unable to obtain full texts for four studies, and translation was not possible for a further five studies; this left 389 reports, which were assessed for inclusion. We included 113 studies (3351 participants) reported in 131 unique publications, with a total of 203 sets of 2 × 2 data reported in these studies.

Study characteristics

The included studies were published between 1990 and 2019. Studies were conducted in the UK ($n = 19$), Italy ($n = 13$), Argentina ($n = 10$), Spain ($n = 9$), Sweden ($n = 8$), the USA ($n = 8$), Canada ($n = 6$), India ($n = 4$), Pakistan ($n = 4$), Islamic Republic of Iran ($n = 4$), Ireland ($n = 3$), the Netherlands ($n = 3$), New Zealand ($n = 2$), Germany ($n = 2$), Brazil ($n = 2$) and Israel ($n = 2$), with single studies from Slovakia, Türkiye, Denmark, France, Finland, Australia, Czechia, Oman, Switzerland, Austria, Egypt, Poland, Lebanon and Serbia. Twenty-nine studies were conducted with adults, 48 with children and 33 with mixed populations of adults and children. Those that did not specify the age of included participants were assumed to have included a mixed population. A further three studies reported accuracy data separately for adults and children; these were treated as if they were two separate studies and data were extracted separately for adults and children. When reported, the mean age was 43.6 years (SD 13.9 years, range 13–94 years) for adults and 6.3 years (SD 4.4 years, range 2 months to 19 years) for children. On average, 66% of adults and 52% of children were female. Fifty-six studies were prospective and 57 were retrospective in design (see table S10 in *Report Supplementary Material 1*).

Risk of bias

A total of 137 sets of 2 × 2 data were judged to be at high risk of bias, 22 were judged to be at low risk of bias and 44 were judged to be at unclear risk of bias (see *Appendix 18*, *Figure 57*, and table S11 in *Report Supplementary Material 1*).

The main reason for sets of 2 × 2 data being judged as having a high risk of bias was because biopsy results were interpreted with knowledge of (or not explicitly blinded to) serology results; this was the case for 118 sets of 2 × 2 data. In 28 sets of 2 × 2 data, there was potential for partial verification bias because not all patients, particularly those with a negative test result, underwent biopsy to verify their true disease status. A further 23 sets of 2 × 2 data were judged as having a high risk of bias because of concerns about patient selection (e.g. through inappropriate study exclusions or patients not adhering to a gluten-free diet prior to testing) and 12 sets were judged as having a high risk of bias because of concerns about the index test (e.g. threshold not prespecified).

Twenty-four sets of 2 × 2 data were judged to be at an unclear risk of bias because of missing information on patient selection (e.g. study exclusion criteria), 23 sets were judged to be at an unclear risk of bias because details of serological testing (e.g. threshold for test positivity) were not reported

and 40 sets were judged to be at an unclear risk of bias because information on flow and timing (e.g. interval between serology and biopsy, or whether or not patients maintained a gluten-free diet between tests) was not reported. The prevalence of CD varied greatly between studies, ranging from 1.8% to 92.6%.

Accuracy of serological tests for diagnosing coeliac disease

All thresholds

The raw 2 × 2 data extracted from each study, together with details on test and test positivity threshold, are summarised in table S10 (see *Report Supplementary Material 1*). The ranges in the estimates of sensitivity, specificity, and positive and negative predictive values are summarised in *Table 8*. The most commonly evaluated test was IgA tTG, which was evaluated in 27 studies with adults[76–114] and in 37 studies with children.[115–151] The next most frequently evaluated test was IgA EMA, which was evaluated in 19 studies with adults[77,81,83,87,88,90,91,93,97,100,107,108,110–112,152–162] and in 28 studies with children.[82,97,108,115,117,118,121–123,131–133,140,144,145,147,151,152,154–157,163–174]

TABLE 8 Study estimates of test accuracy, stratified by age group and test

Serological test	Studies (*n*)	Participants (*N*) (with CD, *n*)	Threshold	Sensitivity (range) (%)	Specificity (range) (%)
Adults					
IgA tTG	27	11,355 (2566)	5–25 U/ml	35–100	0–100
IgG tTG	1	65 (14)	10 U/ml	71	96
IgA EMA	19	7122 (1028)	1 : 5–1 : 20	61–100	88–100
IgG EMA	1	96 (28)	1 : 20	39	99
IgA DGP	3	885 (154)	10–20 U/ml	86–98	92–96
IgG DGP	4	1046 (217)	10–20 U/ml	90–97	99–100.0
IgA/IgG DGP	4	1161 (280)	20 U/ml	86–98	96–98.8
IgA/IgG tTG/DGP	3	1849 (173)	20 U/ml	72–96	80–97.4
IgA actin antibodies	2	820 (140)	25 U/ml	80–86	92–95.1
Children					
IgA tTG	37	7944 (4164)	3–100 U/ml	29–100	8–100
IgG tTG	5	599 (278)	3–7 U/ml	31–97	71–100
IgA/IgG tTG	2	742 (282)	6–45.1 U/ml	94–96	86–99
IgA EMA	28	4974 (2472)	1 : 5–1 : 40	40–100	29–100
IgA/IgG EMA	2	173 (131)	1 : 2.5–1 : 5	95–96	74–91
IgA DGP	1	212 (109)	20 U/ml	85	88
IgG DGP	3	1135 (669)	10–25 U/ml	77–92	84–94
IgA/IgG DGP	6	941 (464)	16–20 U/ml	88–100	22–96
IgA/IgG tTG/DGP	4	986 (415)	3–32.7 U/ml	88–98	61–99

TABLE 8 Study estimates of test accuracy, stratified by age group and test (*continued*)

Serological test	Studies (*n*)	Participants (*N*) (with CD, *n*)	Threshold	Sensitivity (range) (%)	Specificity (range) (%)
Mixed or unspecified					
IgA tTG	25	4564 (1414)	2–89.5 U/ml	38–100	9.5–100
IgG tTG	2	432 (122)	10–18.9 U/ml	41–85	78.0–89
IgA/IgG tTG	1	254 (26)	7.8 U/ml	92	82.9
IgA EMA IgA DGP	15	2884 (843)	1 : 2.5–1 : 10	68–100	38.9–100
IgG DGP	2	561 (58)	19.9 U/ml	77–90	93.4–97
IgA/IgG DGP	2	562 (56)	19.9 U/ml	76–80	92.0–99
IgA actin antibodies	3	480 (48)	NR	71–86	92.9–99

NR, not reported.

Study estimates of sensitivity and specificity at the most commonly reported thresholds are shown in ROC space in *Figures 5* and *6*. These plots also show SROC curves, which are based on all data (i.e. including studies reporting at other thresholds). There was substantial variation in estimates of accuracy across included studies, particularly for IgA tTG and IgA EMA, the most commonly evaluated tests. This made it difficult to draw conclusions regarding the accuracy of these tests. Owing to the range in thresholds used to define a positive test result, it was not appropriate to produce pooled estimates of sensitivity and specificity based on all studies.

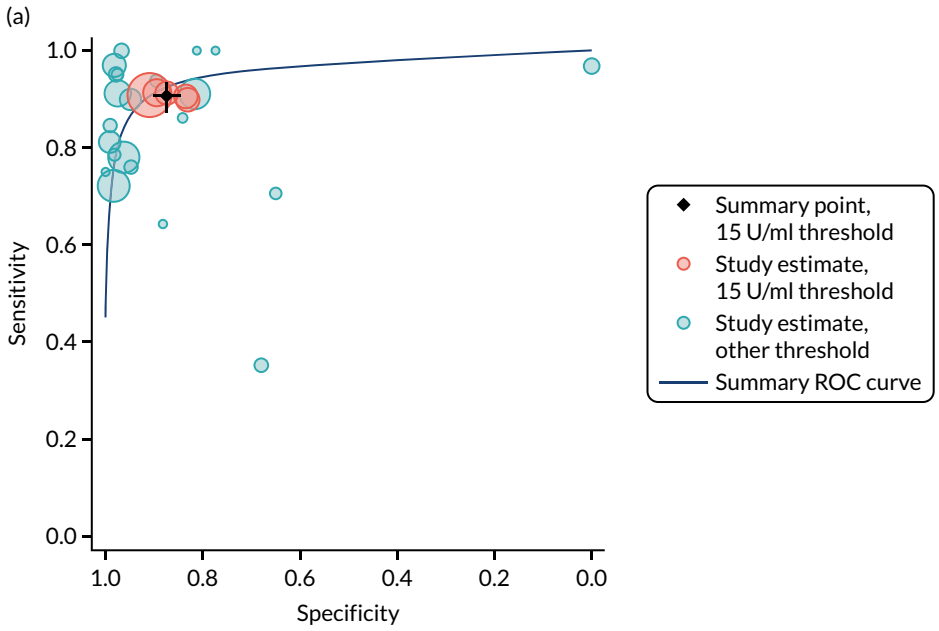

FIGURE 5 Study estimates of test sensitivity and specificity among adults plotted in ROC space. (a) IgA tTG; (b) IgA EMA; (c) IgA DGP; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

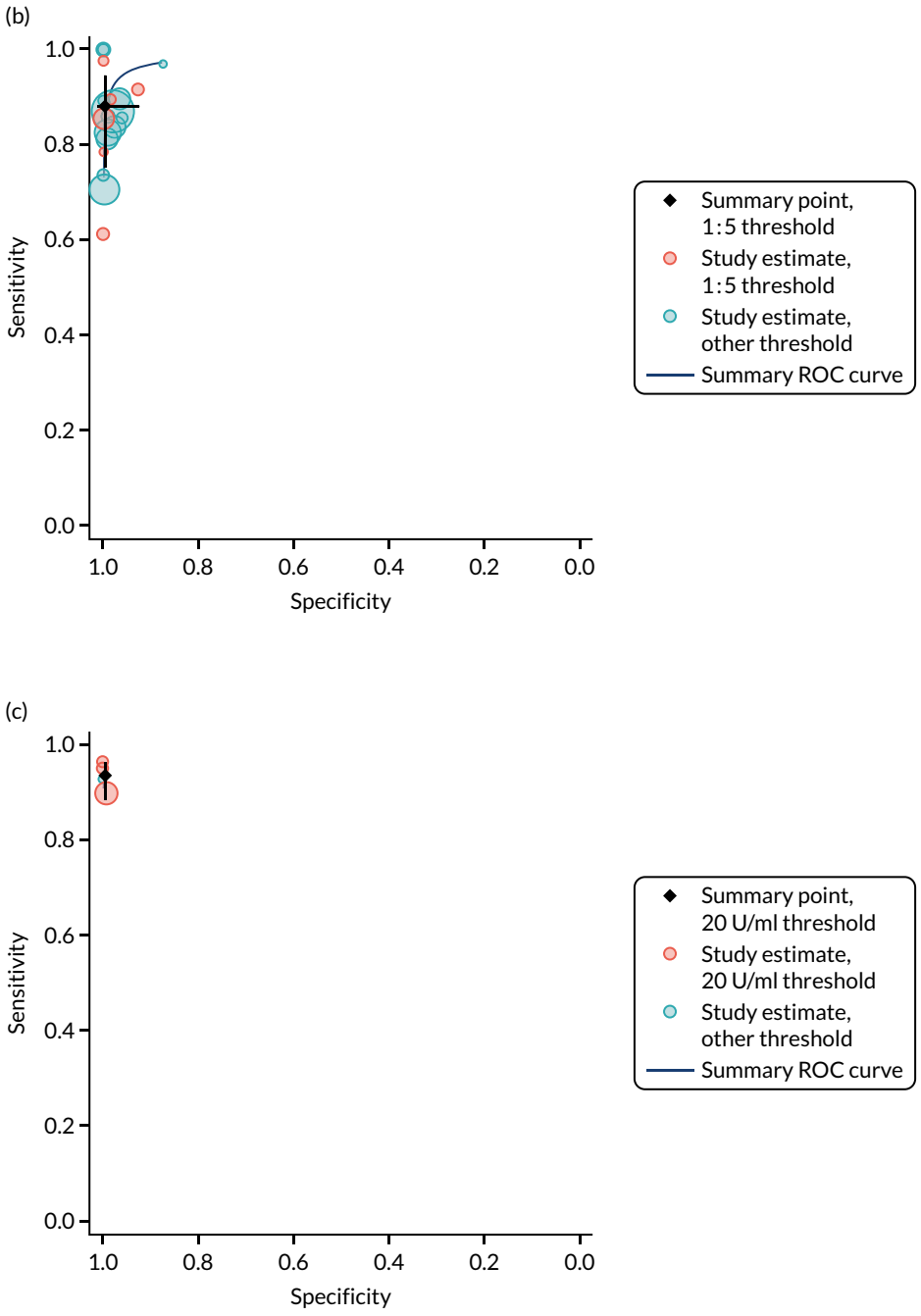

FIGURE 5 Study estimates of test sensitivity and specificity among adults plotted in ROC space. (a) IgA tTG; (b) IgA EMA; (c) IgA DGP; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

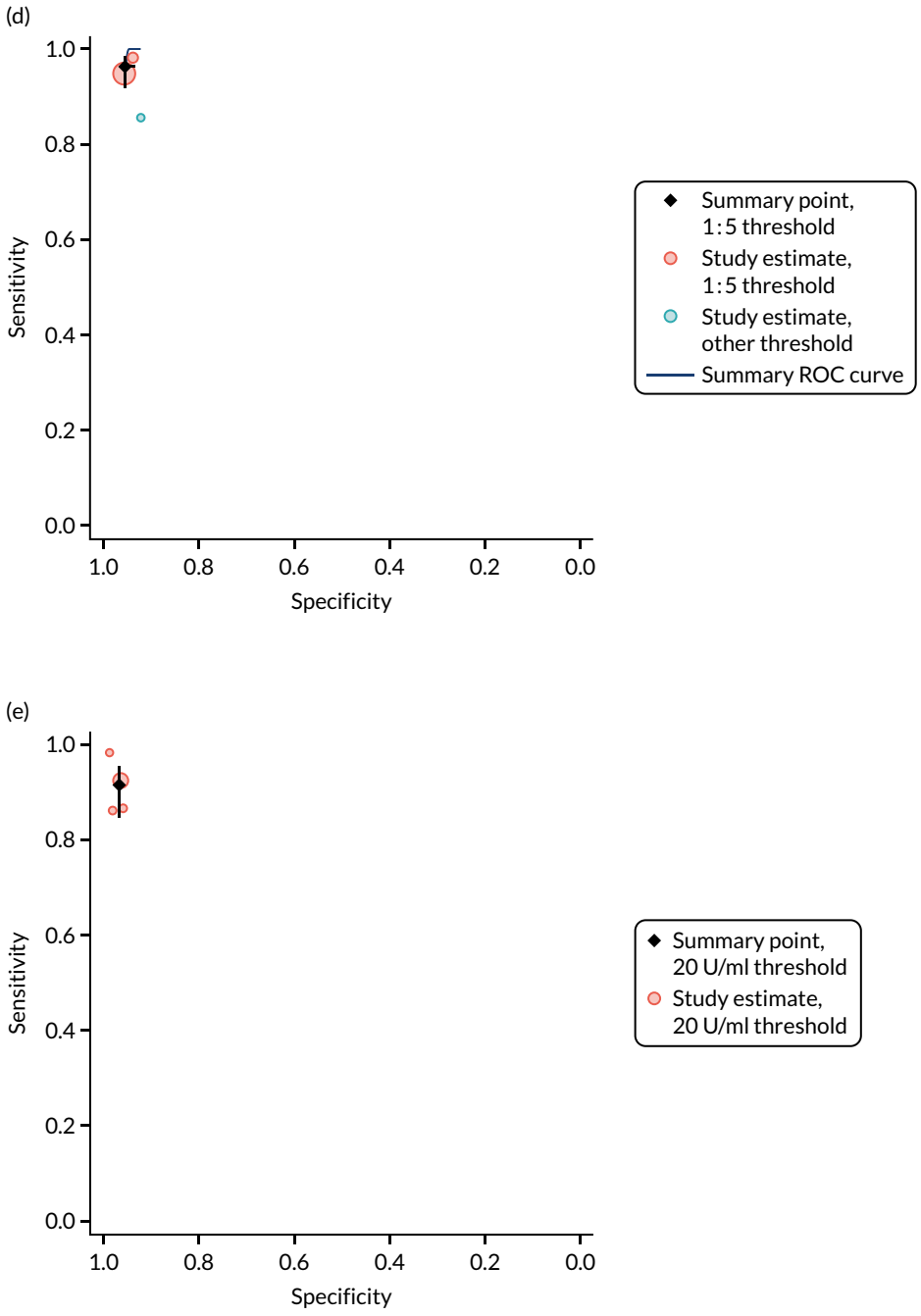

FIGURE 5 Study estimates of test sensitivity and specificity among adults plotted in ROC space. (a) IgA tTG; (b) IgA EMA; (c) IgA DGP; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

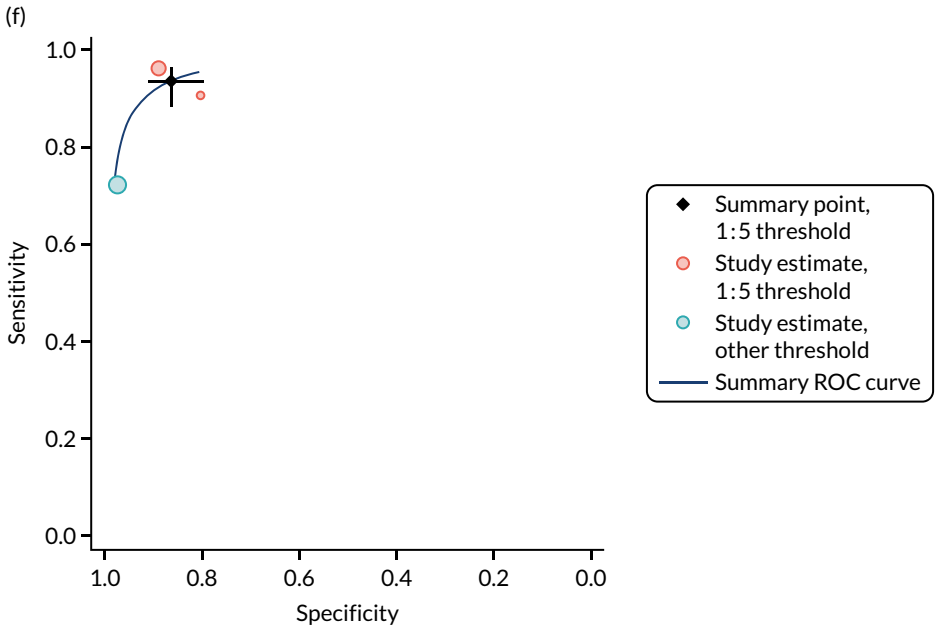

FIGURE 5 Study estimates of test sensitivity and specificity among adults plotted in ROC space. (a) IgA tTG; (b) IgA EMA; (c) IgA DGP; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only.

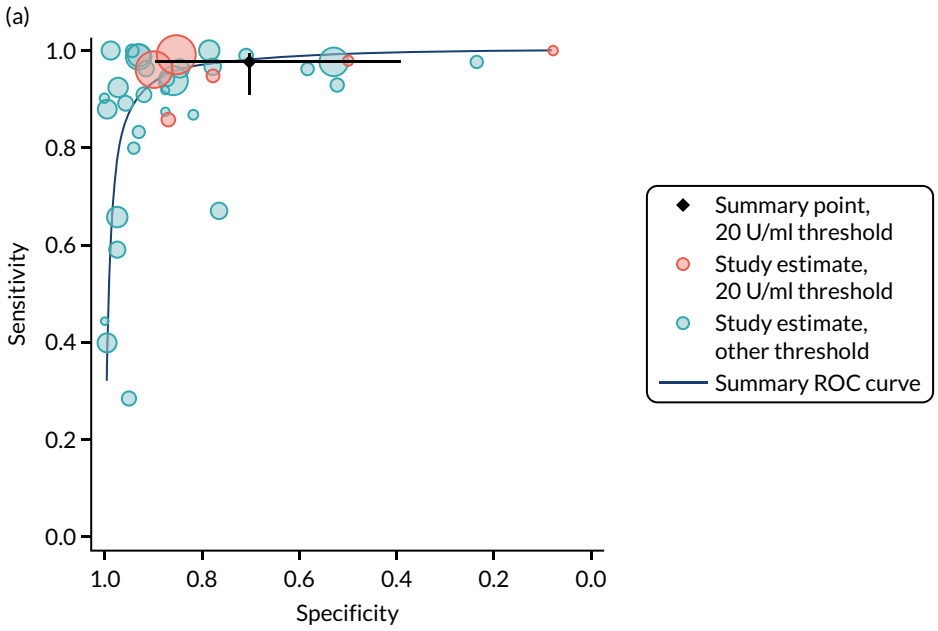

FIGURE 6 Study estimates of test sensitivity and specificity among children plotted in ROC space. (a) IgA tTG; (b) IgG tTG; (c) IgA EMA; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

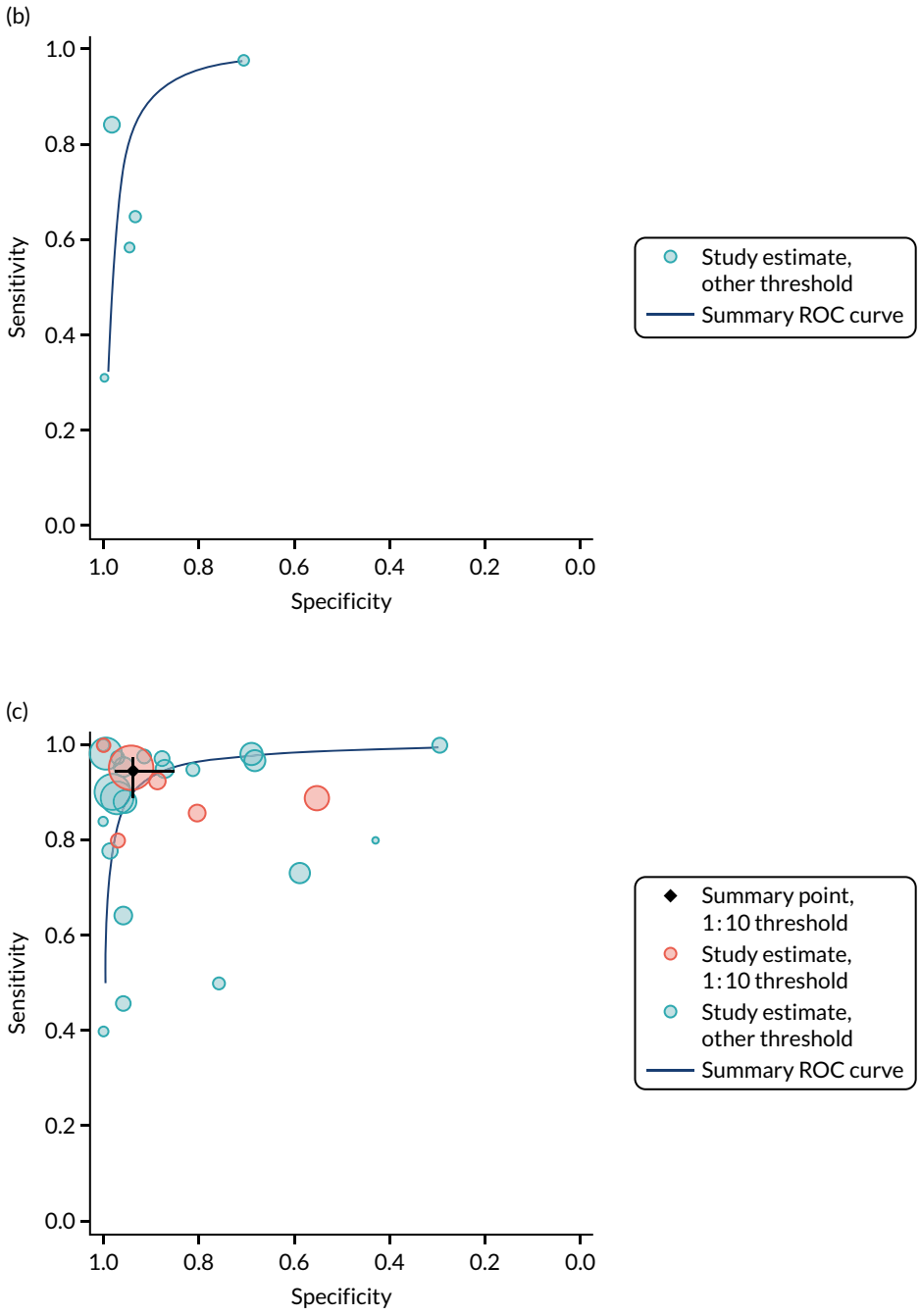

FIGURE 6 Study estimates of test sensitivity and specificity among children plotted in ROC space. (a) IgA tTG; (b) IgG tTG; (c) IgA EMA; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

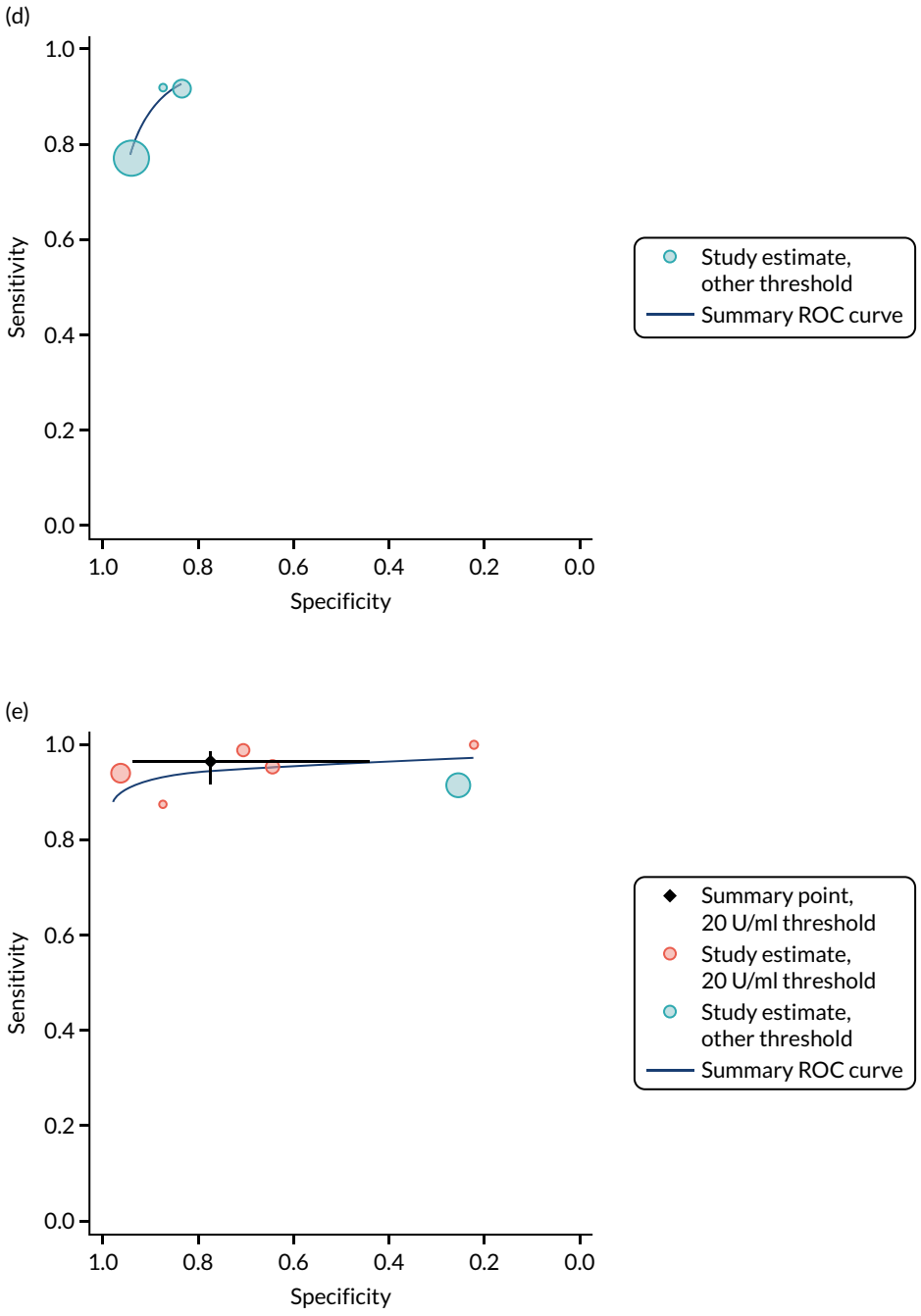

FIGURE 6 Study estimates of test sensitivity and specificity among children plotted in ROC space. (a) IgA tTG; (b) IgG tTG; (c) IgA EMA; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only. (*continued*)

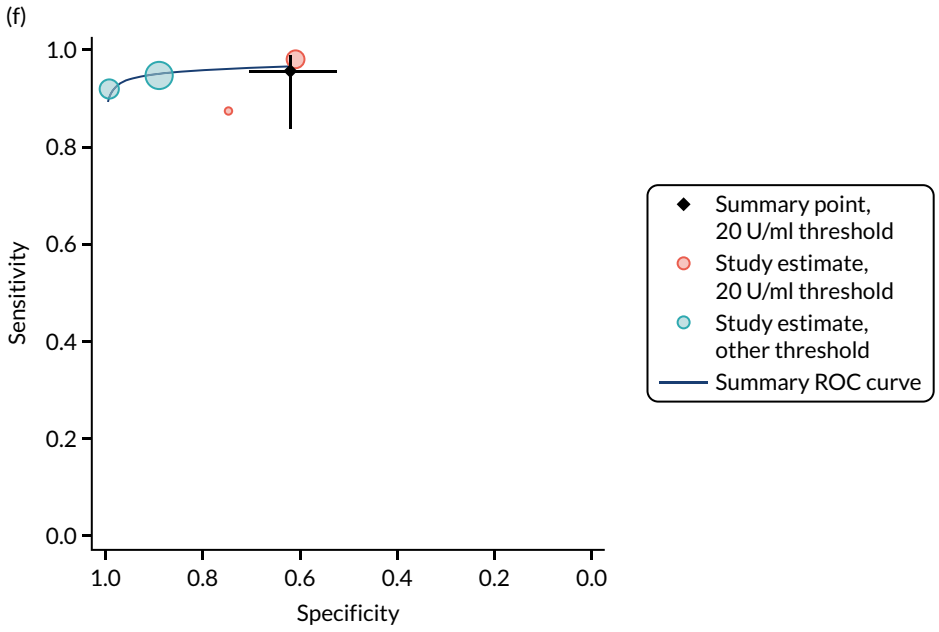

FIGURE 6 Study estimates of test sensitivity and specificity among children plotted in ROC space. (a) IgA tTG; (b) IgG tTG; (c) IgA EMA; (d) IgG DGP; (e) IgA/IgG DGP; and (f) IgA/IgG tTG/DGP. SROC curves are estimated from a meta-analysis of all data, across thresholds. Summary point estimates are estimated from a meta-analysis of data reporting at the most commonly reported threshold only.

Accuracy of tests at the most commonly reported thresholds

Table 9 shows pooled estimates of the accuracy of each serological test evaluated at the most commonly reported threshold. Summary estimates restricted to the most common threshold are also shown in *Figures 5* and *6*.

TABLE 9 Summary estimates of sensitivity and specificity, restricted to the most commonly reported threshold only

Serological test	Studies (*n*)	Participants (*N*) (with CD, *n*)	Threshold	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
Adults					
IgA tTG	5	4310 (454)	15 U/ml	90.7 (87.3 to 93.2)	87.4 (84.4 to 90.0)
IgA EMA	5	927 (446)	1 : 5	88.0 (75.2 to 94.7)	99.6 (92.3 to 100.0)
IgA DGP[a]	2	820 (140)	20 U/ml	96.4 (91.7 to 98.5)	95.4 (93.6 to 96.8)
IgG DGP[a]	3	981 (203)	20 U/ml	93.6 (88.6 to 96.5)	99.4 (98.5 to 99.7)
IgA/IgG DGP	4	1161 (280)	20 U/ml	91.5 (84.7 to 95.4)	96.7 (95.3 to 97.7)
IgA/IgG tTG/DGP[a]	2	851 (155)	20 U/ml	93.5 (88.4 to 96.5)	86.3 (79.7 to 91.0)
IgA actin antibodies[a]	2	820 (140)	25 U/ml	82.9 (75.7 to 88.2)	92.5 (90.3 to 94.3)
Children					
IgA tTG	6	2232 (1051)	20 U/ml	97.7 (91.0 to 99.4)	70.2 (39.3 to 89.6)
IgA EMA	5	1257 (685)	1 : 10	94.5 (88.9 to 97.3)	93.8 (85.2 to 97.5)
IgA/IgG DGP	5	533 (276)	20 U/ml	96.4 (91.7 to 98.5)	77.4 (44.0 to 93.7)
IgA/IgG tTG/DGP[a]	2	244 (133)	20 U/ml	95.6 (83.9 to 98.9)	62.2 (52.8 to 70.7)

a Univariate fixed-effects meta-analysis.

Although tTG was evaluated in 27 studies with adults, only five studies reported at a common threshold of 15 U/ml.[90,100,110,175,176] At this threshold, IgA tTG had a summary sensitivity of 90.7% (95% CI 87.3% to 93.2%) and summary specificity of 87.4% (95% CI 84.4% to 90.0%) for CD among adults (see *Table 9*). Only 5 of the 19 studies of IgA EMA among adults reported accuracy data at a common threshold of 1 : 5.[83,93,107,111,112] These studies reported that the EMA was highly specific, with a summary specificity of 99.6% (95% CI 92.3% to 100%) in adults, but summary sensitivity was lower, at 88.0% (95% CI 75.2% to 94.7%). IgA and IgG DGP also showed very good sensitivity, with summary estimates for IgA, IgG and IgA/IgG DGP all > 90%, but these were evaluated in four or fewer studies.[91,101,109] Specificity for these tests was also high, with all estimates > 95%.

Six of the 37 studies with children reported data at a common threshold of 20 U/ml.[121,134,136,140,141,146] These studies found that IgA tTG was very sensitive, with a summary sensitivity of 97.7% (95% CI 91.0% to 99.4%), but summary specificity was lower, at 70.2% (95% CI 39.3% to 89.6%). Six of the 28 studies of EMAs with children reported data at a threshold of 1 : 10.[121,135,140,144,163,174] Summary sensitivity was 94.5% (95% CI 88.9% to 97.3%) and summary specificity was 93.8% (95% CI 85.2% to 97.5%). IgA/IgG DGP was also evaluated at a common threshold of 20 U/ml in five studies and showed good sensitivity (summary estimate 96.4%, 95% CI 91.7% to 98.5%), but poorer specificity (summary estimate 77.4%, 95% CI 44% to 93.7%).[124,128,136,138,145,150]

Direct comparisons and test combinations

Comparative accuracy studies provided little evidence of differences in accuracy between tests (*Table 10*). Fourteen studies with adults and 16 studies with children provided direct comparison of IgA tTG and IgA EMA. There was a suggestion that IgA EMA was more specific than IgA tTG in adults, with similar estimates of sensitivity; estimates in children were similar for both tests. However, studies reported results at different thresholds and, therefore, formal statistical comparison was not appropriate.

Other test pairs were compared directly in only three or four studies. IgG DGP and IgA/IgG DGP appeared to be slightly more sensitive and specific than IgA tTG; however, this difference was much smaller than indirect comparisons suggested (see *Table 10*). This suggests that studies providing a direct comparison between DGP and other serological tests may be subject to bias, resulting in overestimated accuracy for all tests evaluated in these studies.

A subset of the studies that provided a direct comparison of IgA tTG with IgA EMA also reported data that could be used to estimate the accuracy of these tests when used in combination. We identified six such studies with adults[81,82,88,90,107,108] and six with children.[82,108,121,123,144,145] However, none of these reported accuracy estimates for the same thresholds. We therefore selected the studies that were judged to be at lowest risk of bias and that had the largest sample sizes. These were Hopper *et al.*[90] ($n = 2000$ adults) and Wolf *et al.*[121] ($n = 949$ children). Wolf *et al.*[121] was judged to be at low risk of bias for all domains; Hopper *et al.*[90] was judged to be at low risk of bias for all domains except the reference standard domain, as it was unclear whether or not the reference standard results were interpreted without knowledge of the index test results. We consider these studies to provide the most reliable comparative estimates of the accuracy of IgA tTG and IgA EMA, alone and in combination, among adults and among children. *Table 11* summarises the accuracy data from these studies; these estimates of accuracy were selected for inclusion in the economic model (see *Chapter 8*). Among both adults and children, the IgA tTG test had the highest sensitivity, although estimates among children were very similar, and the IgA EMA test had the highest specificity. There was little improvement in either sensitivity or specificity when the tests were used in combination. Despite thresholds being the same as those used in the meta-analyses for the individual tTG and EMA tests, there were minor differences between estimates from these studies and summary estimates when all studies that reported at the same thresholds were pooled (*Table 12*).

TABLE 10 Study estimates of sensitivity and specificity, restricted to comparative studies only

Serological test	Studies (*n*)	Participants (*N*) (with CD, *n*)	Threshold (range)	Sensitivity (range) (%)	Relative sensitivity (range) (%)	Specificity (range) (%)	Relative specificity (range) (%)
Adults							
IgA tTG vs. IgA EMA	14	6575 (881)					
IgA tTG			5–25 U/ml	64–100		81–99	
IgA EMA			1 : 5	61–100	0.81–1.22	88–100	1.00–1.17
IgA tTG vs. IgA DGP	3	885 (154)					
IgA tTG			10–20 U/ml	64–95		88–98	
IgA DGP			10–20 U/ml	86–98	1.04–1.33	92–96	0.96–1.04
IgA tTG vs. IgG DGP	4	1046 (217)					
IgA tTG			10–20 U/ml	64–95		88–98	
IgG DGP			10–20 U/ml	90–96	0.99–1.44	99–100	1.02–1.13
IgA tTG vs. IgA/IgG DGP	4	1161 (280)					
IgA tTG			5–20 U/ml	76–95		95–99	
IgA/IgG DGP			20 U/ml	86–98	1.01–1.14	96–99	0.99–1.01
Children							
IgA tTG vs. IgA EMA	16	3021 (1746)					
IgA tTG			5.5–21 U/ml	29–99		24–100	
IgA EMA			1 : 5 to 1 : 10	50–100	0.91–2.25	29–100	0.76–1.25

TABLE 11 Estimates of accuracy for the two selected studies that provided information on the accuracy of the tests when used in combination

Study	Population	Participants with complete data (*n*)	Test	Threshold	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
Hopper *et al.*[90] 2008	Adults	2000	Both positive	• 15 U/ml (tTG) • 1 : 4 (EMA)	86 (76 to 92)	99 (98 to 99)
			Either positive	• 15 U/ml (tTG) • 1 : 4 (EMA)	92 (84 to 96)	90 (89 to 92)
			tTG	15 U/ml	91 (82 to 95)	91 (90 to 92)
			EMA	1 : 4	87 (78 to 93)	98 (97 to 99)
Wolf *et al.*[121] 2017	Children	873	Both positive	• 20 U/ml (tTG) • 1 : 10 (EMA)	95 (93 to 97)	95 (92 to 97)
			Either positive	• 20 U/ml (tTG) • 1 : 10 (EMA)	97 (95 to 98)	89 (86 to 92)
			tTG	20 U/ml	97 (95 to 98)	89 (86 to 92)
			EMA	1 : 10	96 (94 to 97)	94 (91 to 96)

TABLE 12 Study estimates of sensitivity and specificity limited to specific subgroups, stratified by age group and test

Serological test	Studies (*n*)	Participants (*N*) (with CD, *n*)	Threshold (range)	Sensitivity (range) (%)	Specificity (range) (%)
Symptomatic patients only					
Adults					
IgA tTG	7	4244 (325)	5–20 U/ml	64–100	88–98
IgA EMA	8	3786 (327)	1 : 5–1 : 20	61–100	98–100
Children					
IgA tTG	8	1126 (615)	4–20 U/ml	40–100	8–100
IgA EMA	8	1327 (753)	1 : 5–1 : 20	40–98	43–100
All patients underwent biopsy					
Adults					
IgA tTG	26	11,183 (2444)	5–25 U/ml	64–100	0–100
IgA EMA	18	7010 (1021)	1 : 5–1 : 20	61–100	88–100
Children					
IgA tTG	31	5824 (3330)	3–100 U/ml	29–100	24–100
IgA EMA	22	3685 (2015)	1 : 5–1 : 40	46–100	29–100
Low risk of bias					
Adults					
IgA tTG	5	1577 (426)	5–20 U/ml	76–100	88–98
IgA EMA	2	268 (103)	1 : 5–1 : 20	61–89	100–100
Children					
IgA tTG	4	1319 (823)	20–21 U/ml	95–100	24–99
IgA EMA	1	873 (528)	1 : 10	95	94

Sensitivity analyses

Table 12 shows results from the sensitivity analyses; further details are reported in *Appendix 19* (see *Figures 58–61*). Estimates of sensitivity and specificity in analyses were restricted to studies of symptomatic patients, studies judged to be at low risk of bias overall on the QUADAS-2 tool and studies in which all patients received a biopsy to confirm whether or not they had CD were similar to the estimates of analyses that included all studies. There were insufficient studies to allow comparisons when analyses were restricted to those that reported a common threshold.

Chapter 6 Accuracy of genetic tests for coeliac disease

We conducted a systematic review of the accuracy of genetic tests for CD. We had originally planned to include this as part of the review of the accuracy of serological tests but decided that these tests were sufficiently different from serological tests that a separate review would be appropriate. The review followed recommendations from the Centre for Reviews and Dissemination[22] and the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0*[23] and is reported in accordance with the PRISMA-DTA statement.[24]

Systematic review methods

Eligibility criteria

We included studies that met the following criteria:

- Study design – diagnostic cohort/cross-sectional studies (also known as 'one-gate design')[25] or diagnostic case–control studies (also known as 'two-gate' or 'multigate' designs).
- Participants – adults and/or children representative of the general population. Studies restricted to specific disease populations without healthy participants were excluded.
- Index test – *HLA-DQ2* and *HLA-DQ8* genetic tests. Studies had to evaluate both markers to be included.
- Reference standard – CD diagnosis, detected by one or more serological tests, including IgA/IgG tTG, EMA or DGP and/or duodenal biopsy. All participants had to be tested for CD.

Studies were included only if sufficient data could be extracted to construct cross-tabulations of the number of people positive for either *HLA-DQ2* or *HLA-DQ8* against the number of people with and people without CD according to the reference standard.

We excluded studies published before 1997 (the year in which tTG was developed), to reduce the variation in CD diagnostic tests.

Search strategy

Studies were identified through the same search as used to identify diagnostic indicators (see *Chapter 3*). Full details of the search strategy are reported in *Appendix 1*.

Study selection

Study selection was conducted in two stages using forms developed in Microsoft Access that were piloted before use. Search results were exported from EndNote in a format that could be imported into Microsoft Access. At stage 1 of study selection, titles and abstracts were screened against the inclusion criteria to exclude papers that were clearly irrelevant. At the second stage, full texts identified as possibly relevant in the initial screening were assessed in detail and reasons for exclusion were documented. Both stages of study selection were performed independently by two reviewers, and disagreements about study eligibility were resolved through discussion or by consulting a third member of the review team.

Data collection process

Standardised data extraction forms were developed using Microsoft Access. These were piloted on a small sample of papers and adapted as necessary before use. Data extraction was performed by one reviewer and checked by a second, with disagreements resolved through discussion or referral to a third reviewer.

We extracted the following data from each included study:

- study characteristics (design, location, setting)
- participant characteristics (age, sex)
- details on the HLA test
- reference standard test used to confirm the diagnosis of CD.

Results data were extracted as 2 × 2 tables of test results (numbers of true positives, false negatives, false positives and true negatives) for the presence of either *HLA-DQ2* or *HLA-DQ8* against the reference standard of serological tests or biopsy (*Table 13*).

Risk of bias

Risk of bias was assessed using the QUADAS-2 tool.[28] We removed the index test domain signalling question ('If a threshold was used, was it prespecified?'), as HLA genotyping does not involve a threshold. We also removed the flow and timing domain signalling question ('Was there an appropriate interval between index test and reference standard?'), as the HLA genotyping result will not change over time: you are either born with or without a particular genotype. Therefore, test accuracy will not be influenced by time between genotyping and when the reference standard is performed.

Synthesis of results

We present a narrative summary of the included studies, including a summary of the characteristics of the included studies (e.g. study design, population size, geographical location, year, population characteristics, genetic test details and CD diagnosis). We also describe the main methodological problems or biases that affected the studies.

We had intended to stratify our analysis according to whether studies were conducted with adults or children, but there were no studies with adults. A bivariate random-effects meta-analysis was fitted, assuming binomial likelihoods for the numbers of true positives and true negatives in each study.[29,30] Pooled estimates of sensitivity and specificity and estimates of the between-study SD sensitivity and specificity on the logit scale (tau) are reported. We present study-specific and pooled estimates of sensitivity and specificity in coupled forest plots (see *Figure 7*). We conducted sensitivity analyses to restrict our analysis to studies judged to be at low risk of bias.

Results of assessment of diagnostic accuracy of indicators

Full details of the search results are reported in *Chapter 3*. We identified four studies reported in six publications ($n = 12{,}087$);[177–182] one study, based on the Dutch Generation R birth cohort study, was reported in three publications.[180–182] Although none of these specifically aimed to evaluate the accuracy of HLA testing for CD, all reported data that could be used to estimate accuracy of HLA testing. We selected the most recent report, which also provided data on the greatest number of participants, for inclusion in the analysis.[180]

Study characteristics

Table 14 provides an overview of the included studies. All studies were conducted with children. Two studies used a nested case–control design and two used a cohort design. The median age was 12 years in two studies,[178,179] 6 years in one study[180] and 3 years in the remaining study.[177] Two studies

TABLE 13 Extracting results data

HLA-DQ haplotypes	CD	No CD
HLA-DQ2 or *HLA-DQ8*	True positive	False positive
Negative for *HLA-DQ2* and *HLA-DQ8*	False negative	True negative

TABLE 14 Details of studies that evaluated the accuracy of HLA genotyping

Study	Population	Study design	Genetic test details	Total sample (*N*) (analysed, *n*)	Age (years)	Sex (% female)	Control group	Reference standard	Setting	Location	Risk of bias
Björck *et al.*[177] (2010)	Children	Nested case–control	*HLA-DQ2*, *HLA-DQ8* or both	3435 (3435)	3	NR	Cases: HLA positive Controls: HLA negative	Serology and only positive patients biopsied	Community	Sweden	Low
Mäki *et al.*[178] (2003)	Children	Cohort	*HLA-DQ2*, *HLA-DQ8* or both	3654 (3617)	Median 12 (range 7–16)	NR	NA	Serology and only positive patients biopsied	Community	Finland	Low
Sandström *et al.*[179] (2013)	Children	Nested case–control	*HLA-DQ2*, *HLA-DQ8* or both	1320	12	52	Cases: serology positive, referred for biopsy Controls: serology negative	Serology and only positive patients biopsied	Community	Sweden	Low
Wahab *et al.*[180] (2019)	Children	Cohort	*HLA-DQ2*, *HLA-DQ8* or both	4442 (3715)	Median 6 (range 5–9)	48	NA	tTG positive	Community	The Netherlands	High

NA, not applicable.

were conducted in Sweden,[177,179] one in Finland[178] and one in the Netherlands. Three studies[177–179] confirmed the diagnosis of CD by a combination of serology with biopsy of those who were positive on serology, the other used serology alone.[180]

Risk of bias

Three studies were judged to be at low risk of bias across all domains (see *Appendix 20*, *Figure 62*).[177–179] The other was judged to be at high risk of bias as CD diagnosis was based on serology alone.[180] This study was judged to be at low risk of bias for all other QUADAS-2 domains.

Accuracy of diagnostic indicators to detect coeliac disease

Results were broadly consistent across studies, with visual examination of the forest plot (*Figure 7*) and the SROC plot (*Figure 8*) suggesting little evidence of heterogeneity. The presence of either *HLA-DQ2* or *HLA-DQ8* had a very high summary sensitivity of 99.2% (95% CI 83.4% to 100%) and summary specificity of 55.6% (95% CI 50.2% to 60.9%). These figures were included in the economic model in *Chapter 8*.

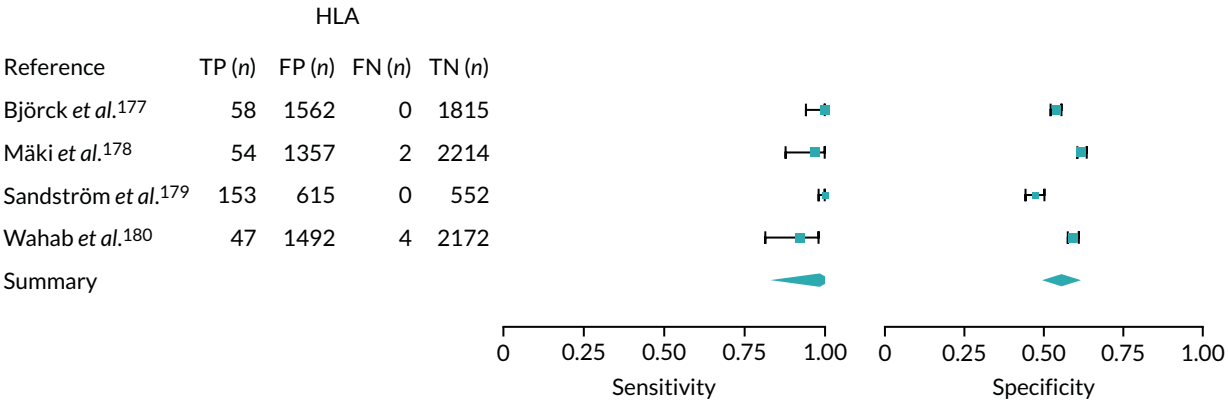

FIGURE 7 Forest plots of individual study and summary estimates of sensitivity and specificity. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

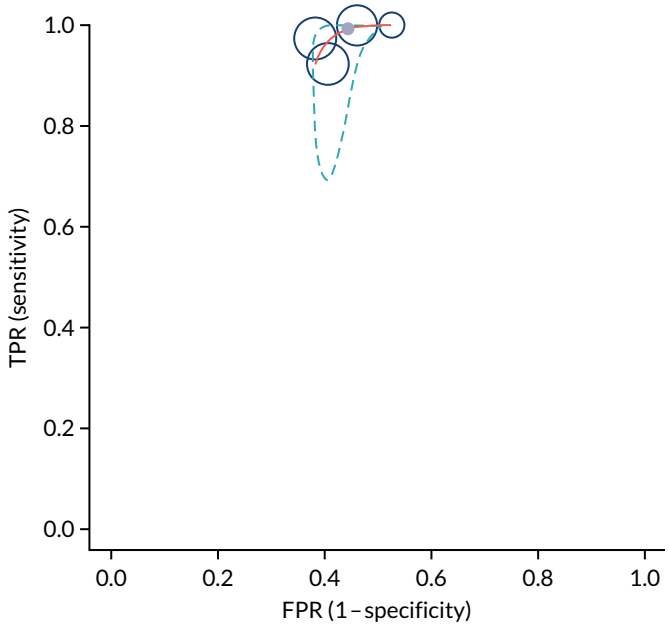

FIGURE 8 The SROC curve for *HLA-DQ2/-DQ8* for diagnosing CD. FPR, false-positive rate; TPR, true-positive rate.

Chapter 7 Establishing diagnostic thresholds

This chapter describes the collaborative work with patients and the public through focus groups and an online survey to investigate how confident people want to be in their diagnosis before starting a gluten-free diet or undergoing a biopsy.

The aims of the survey were as follows:

- to estimate at what level of diagnostic certainty people are willing to start a gluten-free diet without a confirmation biopsy if they are symptomatic
- to estimate at what level of diagnostic certainty people are willing to start a gluten-free diet without a confirmation biopsy if they are asymptomatic
- to understand what factors influenced their answers on the above
- to estimate the quality of life among people with CD
- to understand how strictly people with CD followed the gluten-free diet
- to understand how difficult people with CD found it to follow a gluten-free diet
- to understand the current assumptions and understandings of CD diagnosis and how that affects confidence in diagnosis before starting a gluten-free diet.

Survey development and dissemination methods

Survey development

Three scenarios (described in more detail in the following section) and the survey questions were drafted by a team of researchers and clinicians. The wording and format of the survey were developed in collaboration with the patient representatives on the trial team. The scenarios were turned into short videos, as suggested by the patient representatives, to make them more accessible, using online VideoScribe software (Sparkol Ltd, Bristol, UK). The videos can be accessed on YouTube (YouTube, LLC, San Bruno, CA, USA).[183–185] We organised a focus group with four patient representatives, who commented on the survey questions, the scenarios and the videos. The survey was adapted in accordance with their comments, and the focus group participants were given the opportunity to provide feedback on the revised material. Finally, the survey questions were tested and commented on by a plain-language panel to get the view of people who are less familiar with CD. The survey was amended accordingly.

We used OnlineSurveys (Jisc, London, UK) as the survey platform, which is an online survey tool designed for academic research. OnlineSurveys uses an ISO 27001-certified information security management system[186] and complies with the General Data Protection Regulation.[187] The Faculty of Health Science Research Ethics Committee granted ethics approval for this study.

Survey questions

In the survey, respondents were shown three short videos. Each video explained a different scenario, in which the risk of having CD was different. In the first scenario (video 1), we asked respondents to imagine that they had been suffering from typical symptoms of CD; in the second scenario (video 2), they were asked to imagine that a first-degree relative had been diagnosed with CD; and in the third scenario (video 3), they were asked to imagine that they had been diagnosed with a condition that puts them at greater risk of having CD (see scenario descriptions in *Appendix 21*, *Box 1*). The videos were followed by three or four questions that asked respondents at which part of the diagnostic pathway they would have wanted to start a gluten-free diet: after the first appointment with the GP (low risk of CD based on symptoms or risk conditions alone), after getting a positive blood test result (higher risk of CD) or after a confirmation biopsy (CD diagnosis almost certain). Respondents were given the option to explain their answers in a free-text box. After the respondents went through the three

scenarios, which were designed to help people think about disease risk and certainty of a diagnosis, they were asked what level of certainty of a CD diagnosis they would want from a blood test before they were willing to start a gluten-free diet (in a scenario with and a scenario without symptoms).

At the end of the survey, we asked for some general demographics (age, sex, ethnicity and socioeconomic status). We also asked if the respondents had (or believed they had) CD, and, if so, we had some follow-up questions about their diet and quality of life. Quality of life was assessed using the Coeliac Disease Quality of Life Measure 1.0 (CD-QOL), which is a validated questionnaire containing 20 items across four subscales: limitations, dysphoria, health concerns and inadequate treatment. Psychometric validation has indicated both convergent and discriminate validity of the CD-QOL, and it has been shown to have a high internal consistency and reliability.[188] Finally, respondents had the opportunity to leave any final comments or feedback about the survey in a free-text box. People of all ages could participate, and it was possible to fill out the survey on behalf of a child.

Survey distribution

A dissemination strategy was developed in collaboration with the communications manager at the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) West. We developed copy for tweets, advertisements, newsletters and Facebook posts (Meta Platforms, Inc., Menlo Park, CA, USA). To encourage participation, we said that we would enter respondents into a prize draw for a £50 Amazon voucher (Amazon.com, Inc., Bellevue, WA, USA).

The survey was endorsed by the Coeliac UK charity, which helped promote the survey on its social media platforms.

Fifty-one Facebook groups were contacted, of which the following 20 agreed to promote our survey on their Facebook pages: Coeliacs in Bristol, Healthwatch Bristol, Healthwatch South Gloucestershire, Healthwatch Somerset, Up Your Street, Gluten Free Bristol, BS5 Connect, Bristol Parents Club, Gluten Free Vegans UK, Vegetarian Coeliacs UK, Osteoporosis UK, Wirral Coeliac Support Group, Coeliac in the Scottish Borders, Gluten Free Blogger Group, Grub without Gluten, Coeliac children UK (Plus allergies), Coeliac and Gluten Free in Essex, Healthy eating for kids and family, Coeliac Central and GUTs Group (Coeliac UK's Gluten free Under Thirties). Diabetes UK, Bristol Healthwatch and Healthwatch North Somerset posted our advertisement on their websites.

We contacted 17 organisers of citizen panels, of whom three agreed to help. An advertisement was sent out to Healthier Together Panel, the NHS Lincolnshire Citizens' Panel and the Leicester City Clinical Commissioning Group Citizens' Panel, which are online groups, each of around 1000 people from the local area.

We sent three different tweets from the NIHR ARC West Twitter (Twitter, Inc., San Francisco, CA, USA) account that included the Twitter handles of relevant organisations. Bristol University, Coeliac UK, Healthcare Improvement Scotland – Community Engagement, Healthwatch Bristol and Healthwatch South Gloucestershire agreed to send tweets from their accounts.

The NIHR Centre for Engagement and Dissemination agreed to retweet from the @NIHRinvolvement and @NIHRtakepart accounts and add our survey to its public engagement newsletter. We also promoted our survey through the NIHR ARC West newsletter, the People in Health West of England monthly update *Newsflash*, and the Bristol Population Health Science Institute newsletter.

Finally, a news story was published on the NIHR ARC West website and the University of Bristol newsroom, and we developed a blog with a public contributor, which was published on the NIHR ARC West website and shared on Twitter.

The survey was live for 2 months, from January to March 2021.

Data analysis

The data were exported from the online survey tool. Ethnicity was summarised with a binary variable (white or non-white). Qualifications were recoded, keeping only the highest qualification, using the following order from high to low: college or university degree, Advanced Level or equivalent, Ordinary Level or General Certificate of Secondary Education or equivalent, or other (National Vocational Qualification/Higher National Diploma/Higher National Certificate, professional qualifications or Certificate of Secondary Education). Postcodes were used to link to IMD 2015 deprivation deciles for England,[67] Scottish IMD 2020v2 deciles,[189] Welsh IMD deciles[190] and Northern Ireland deprivation rank converted to decile.[191] Respondents with postcodes indicating that they lived outside the UK were excluded.

Descriptive statistics, including percentages, medians and IQRs, were used to describe the sample. We calculated summary estimates with 95% CIs on the level of certainty respondents want from a blood test before committing to a lifelong gluten-free diet if they had or did not have symptoms. We performed an exploratory analysis to identify possible causes of variation in answers. We performed multiple linear regression to investigate whether or not having a CD diagnosis, being familiar with the gluten-free diet or ever having had a biopsy were associated with the level of certainty people chose. We accounted for age group in the model.

We performed a subset analysis, using descriptive statistics, on all respondents with CD to investigate how difficult they find adhering to the diet and how strictly they adhere to it, and to quantify their quality of life. Quality-of-life measures were calculated according to the standardised CD-QOL previously described.[188] In brief, questions are grouped into four domains: dysphoria, CD-related limitations, health concerns and inadequate treatment. A score is calculated by transforming the Likert scale to a number, summing up the scores per domain, and converting these to a score that ranges from 0 to 100 with formulas supplied by the developers.

To analyse the free-text answers in which respondents could explain their responses to each scenario, we used content analysis to identify themes and patterns as described by Hsieh and Shannon,[192] whereby a bottom-up approach is used to explore qualitative data. Rachel O'Donnell coded the free-text answers and analysed the responses by identifying higher-level recurring themes.

Results

Respondent characteristics

The survey was completed by 472 people. Five respondents did not live in the UK and were removed from the analysis. A total of 244 (52%) respondents had CD, with the condition confirmed by a blood test and/or biopsy. An additional 36 respondents believed that they had CD, although this had not been confirmed by a test. These respondents were included in the group without confirmed CD ($n = 223$, 48%). Thirty-two (6.9%) respondents were children (aged < 18 years); either they filled out the questionnaire by themselves or it was done by a parent on their behalf. The majority of respondents were aged between 26 and 64 years ($n = 310$, 66.2%). Questions on sex, ethnicity, qualifications and postcode were optional; these were answered by most CD patients, whereas most respondents without CD did not answer these questions. Among those who answered the optional questions, the vast majority were white ($n = 264$, 95%) and female ($n = 239$, 86%). Most respondents went to university or college ($n = 159$, 58%). The highest proportion lived in south-west England ($n = 98$, 36%). Respondents tended to live in less deprived areas (median deprivation index of 7) than the national average; this was similar across respondents with and those without CD. A total of 304 (65%) respondents were following a gluten-free diet at the time of filling out the survey and 28 (6%) had done so in the past (see *Appendix 22*, *Table 59*).

Scenarios

The scenario questions were answered by 88.5–90.0% of respondents (*Table 15*). In scenario 1, in which respondents were asked to imagine having typical CD symptoms, 387 (92.8%) respondents opted for a blood test. If the blood test showed a negative result for CD, 223 (53.5%) respondents chose to follow a gluten-free diet anyway to find out if it reduced their symptoms, 93 (22.3%) respondents wanted further testing for CD and 101 (24.2%) accepted that it was unlikely that they had CD. The free-text answers revealed that some respondents misunderstood this question and believed that the negative test result followed two positive test results, which may have affected their answers.

If the test result showed a positive result for CD, corresponding to a 33% risk of having CD, the majority of respondents opted for a confirmation biopsy ($n = 295$, 70.7%), rather than starting a gluten-free diet immediately. If the blood test showed a strong positive result, increasing their risk of CD to 75%, 184 (44.1%) respondents chose to start a gluten-free diet without confirmation biopsy, whereas 224 (53.7%) respondents chose to wait for a biopsy appointment.

In scenario 2, in which respondents were asked to imagine that a first-degree relative had CD, the majority opted for a blood test ($n = 369$, 88.5%). If the test was positive and the risk of CD was 50%, 94 (22.5%) respondents would start a gluten-free diet without a confirmation biopsy, but most ($n = 297$, 71.2%) would opt for a confirmation biopsy. If the test was strongly positive and the risk of CD was 90%, 195 (46.8%) respondents would start the gluten-free diet, whereas 207 (49.6%) respondents still preferred to wait for a confirmation biopsy.

In scenario 3, in which the respondents were asked to imagine being diagnosed with risk conditions that increased their risk of CD to 2%, 376 (90.2%) respondents opted to have the blood test. At 15% and 55% risks of CD, after a positive or strongly positive test result, the majority opted for a confirmation biopsy [$n = 336$ (80.6%) and $n = 311$ (74.6%) for 15% and 55% risks, respectively], rather than starting a gluten-free diet immediately.

Certainty of coeliac disease diagnosis

When respondents were asked to imagine that they had symptoms, they wanted to be a median of 66% (IQR 33–90%) certain of the diagnosis before starting a gluten-free diet. Without symptoms, respondents wanted to be more certain (median 90%, IQR 66–99%) before committing to a gluten-free diet.

TABLE 15 Responses to scenarios

			Preferred option per scenario in response to risk of having CD, *n* (%)		
Scenario	**Risk of CD (%)**	**Test result**	**Start GFD**	**Further testing**	**No further testing or diet**
GI symptoms and fatigue	1	Negative	223 (53.5)	93 (22.3)	101 (24.2)
GI symptoms and fatigue	5	Pre test	21 (5)	387 (92.8)	12 (2.9)
GI symptoms and fatigue	33	Positive	112 (26.9)	295 (70.7)	9 (2.2)
GI symptoms and fatigue	75	Strong positive	184 (44.1)	224 (53.7)	6 (1.4)
First-degree relative	10	Pre test	21 (5)	369 (88.5)	30 (7.2)
First-degree relative	50	Positive	94 (22.5)	297 (71.2)	28 (6.7)
First-degree relative	90	Strong positive	195 (46.8)	207 (49.6)	17 (4.1)
Osteoporosis	2	Pre test	15 (3.6)	376 (90.2)	30 (7.2)
Osteoporosis	15	Positive	51 (12.2)	336 (80.6)	33 (7.9)
Osteoporosis	55	Strong positive	99 (23.7)	311 (74.6)	7 (1.7)

GFD, gluten-free diet.

We found no evidence that age group or having had a biopsy affected the level of certainty of CD diagnosis that respondents would like before starting a gluten-free diet. However, respondents without CD and those familiar with a gluten-free diet accepted a lower certainty. In the scenario in which respondents were asked to imagine that they had symptoms, this was 20% lower for people without CD [standard error (SE) 3.8, $t = -5.1$; $p < 0.001$] and 15% lower for those familiar with a gluten-free diet (SE 4.0, $t = -3.7$; $p < 0.001$). In the scenario in which respondents were asked to imagine that they did not have symptoms, this was 13% lower for people without CD (SE 3.5, $t = -3.7603.8$; $p < 0.001$) and 12% lower for those familiar with a gluten-free diet (SE 3.6; $t = -3.2$; $p = 0.001$) (*Figure 9*).

Gluten-free diet adherence and difficulty

Figure 10 shows the results from CD patients regarding the difficulty of following a gluten-free diet and how strictly they adhered to the diet. A total of 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. Most respondents with confirmed CD reported that they were strict or very strict in their adherence to the gluten-free diet ($n = 222$, 90.6%).

Quality of life among coeliac disease patients

The median overall quality-of-life score among CD patients was estimated at 59.38 (IQR 43.75–76.25), based on the CD-QOL. Quality of life is considered good when the score is > 59, medium when the score is 37–59 and poor when the score is < 37. Although there was large variation between CD patients' quality-of-life scores, most scores indicated a good or medium quality of life (*Figure 11*). CD patients had a high score in the dysphoria domain (median 87.50, IQR 68.75–93.75), suggesting that dysphoria did not affect quality of life for the majority of respondents. CD patients also had a good score in the health concerns domain (median 60.0, IQR 35.0–80.0), although there was more variation, and some respondents felt that their quality of life was affected by health concerns. CD patients had a medium score for the domains 'CD-related limitations' (median 55.56, IQR 36.11–72.22) and 'inadequate treatment' (median 50.00, IQR 37.50–50.00). About one-quarter of the respondents with CD had a low score (associated with a poor quality of life) for the CD-related limitations and health concerns domains.

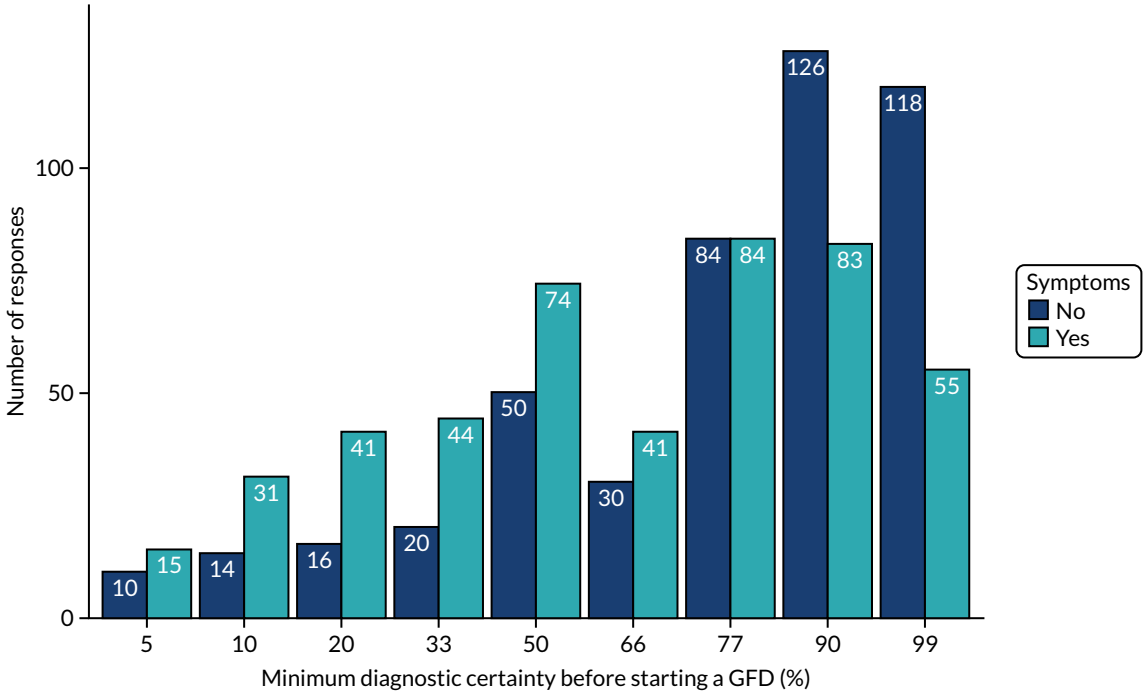

FIGURE 9 Preferred certainty of CD diagnosis before starting a GFD. GFD, gluten-free diet.

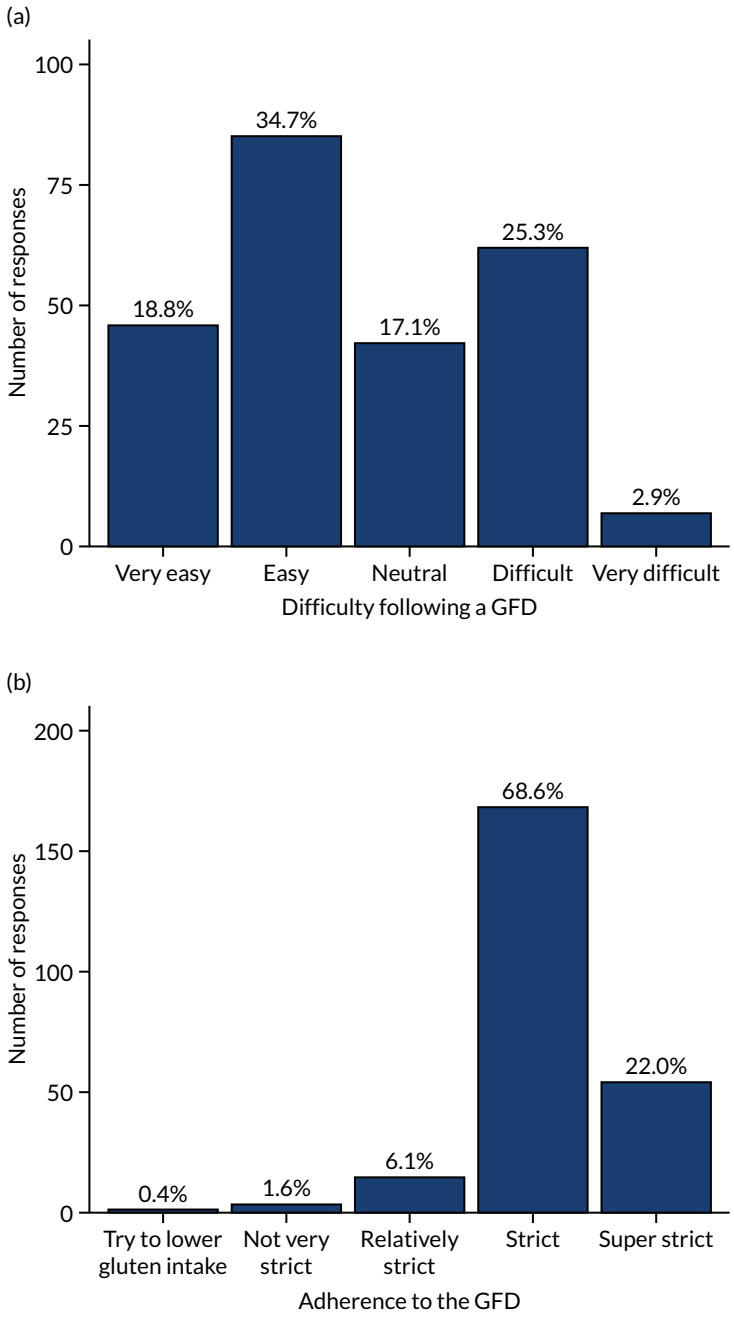

FIGURE 10 Gluten-free diet adherence and difficulty. (a) Difficulty following a GFD; and (b) adherence to a GFD. GFD, gluten-free diet.

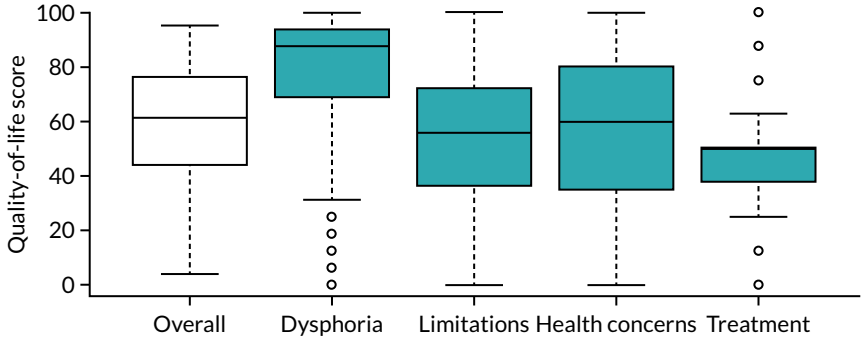

FIGURE 11 Quality-of-life scores (CD-QOL).

Qualitative analysis

Of the 468 respondents, 353 (75.4%) used at least one of the free-text boxes to explain their answer to a scenario question. Of these, 185 (52.4%) had a CD diagnosis confirmed by a blood test and/or biopsy and 167 (47.3%) did not. Of those who answered, the highest proportion fell into the 41–64 years age group (42.2%), followed by the 26–40 years age group (28.0%). Twenty-six children (aged < 18 years), or parents of children (7.4%), explained their answers to the scenario questions. The response rate was slightly higher for those with CD than for without [CD, $n = 17/185$ (9.2%); no CD, $n = 9/167$ (5.4%)] (see *Appendix 22*, *Table 60*).

Free-text analysis

Four key themes and 29 subthemes were identified in the explanations respondents gave. The four key themes were factors that prompt CD diagnosis, the diagnostic process, how to respond to a negative test result and opinions on the gluten-free diet (see *Appendix 23*, *Table 61*). Themes raised by adults and children were similar.

Factors that prompt coeliac disease diagnosis

The most frequently mentioned prompt for seeking CD diagnosis was being diagnosed with osteoporosis, with 44 (9.4%) respondents remarking that this would be a worrying development:

> *If a young man gets an old woman's disease they'd be clutching at lots of straws to try and figure it out.*

Thirty-seven (7.9%) respondents stated throughout the scenarios that the (more general) future risks of CD would prompt seeking or continuing testing for diagnosis. A total of 59 (12.6%) respondents said they would look into CD diagnosis immediately and rule it out early if it was suggested to them by their doctor. For 29 (6.2%) respondents, symptoms would decide whether or not they looked into getting or continuing a diagnosis. Twenty-four (5.1%) respondents said that family has affected them considering a CD diagnosis for themselves.

A total of 49 (10.5%) respondents said that having an official diagnosis is important to them, stating that there are benefits to having an official record:

> *If I have it, I want the diagnosis on my medical records so that I can be allowed DEXA [dual-energy X-ray absorptiometry] scans and flu jabs recommended for people with coeliac disease.*

In contrast, only four (0.9%) respondents said that they felt that there is no point to an official diagnosis:

> *As the 'benefit of having a diagnosis' is irrelevant as gluten-free prescriptions aren't allowed anymore and little no support or understanding from professionals.*

The diagnostic process

A total of 184 (39.3%) respondents mentioned that they wanted or were happy to have a blood test for CD, as it is not invasive and is seen as easy to have:

> *It is easy and quick to get a blood test done which would give a much clearer idea of the situation.*

As for opinion on biopsies, 116 (24.8%) respondents said they feel that a biopsy is necessary for confidence in their diagnosis, whereas 27 (5.8%) feel that biopsy is invasive or unpleasant and would want to avoid it. The majority of those who believe that a biopsy is necessary for certainty of their diagnosis are those with CD [CD, $n = 77$ (31.63%); no CD, $n = 39$ (17.5%)]. Forty-one (8.8%) respondents said they would continue a gluten diet for biopsy even if they did not have symptoms. A total of 76 (16.2%) respondents mentioned that, when having no symptoms, a biopsy was more

important for confidence in diagnosis and they were more willing to continue a gluten-containing diet during the waiting time for a biopsy appointment.

Twenty-eight (6.0%) respondents stated that 6–8 weeks is an acceptable wait time for a biopsy, compared with 13 (2.8%) who stated that the wait time was unacceptable, and 76 (16.2%) respondents expressed that, if the blood test showed a > 50% chance of having CD, they would start a gluten-free diet without waiting for a biopsy:

> *This is a very high answer from a blood test. I feel I have got the answer I need without needing an invasive biopsy.*

How to respond to a negative test result

When presented with a negative or low chance of having CD, 37 (7.9%) respondents said that they would try a gluten-free diet regardless of diagnosis:

> *If the gluten-free diet could potentially stop the pain or improve quality of life I would start the diet regardless of diagnosis.*

Thirty-two (6.8%) respondents would ask for further testing or retesting if they had a negative result. A total of 26 (5.6%) respondents commented that their doctor's guidance and opinion would be important to them, and 26 (5.6%) respondents would accept not having CD.

Opinions on a gluten-free diet

A total of 128 (27.4%) respondents stated that they would want a definitive diagnosis (through a biopsy) before starting a gluten-free diet, whereas 36 (7.7%) would start a gluten-free diet without a definitive diagnosis.

Twenty-seven (5.8%) respondents said that the lowest likelihood of having CD would not be enough for them to start a gluten-free diet, and 25 (5.3%) stated that a 50/50 likelihood would not be enough to start a gluten-free diet. However, 20 (4.3%) would start a gluten-free diet at the lowest likelihood (≤ 10% chance) of having CD. The majority of those who stated this were those without a CD diagnosis [CD, $n = 1$ (0.2%); no CD, $n = 19$ (8.5%)]:

> *I would want my symptoms to get better as soon as possible, so if the [gluten-free diet] helped to eliminate the uncomfortable symptoms, that would be good enough for me. I wouldn't need the tests.*

A total of 77 (16.5%) respondents said they would start a gluten-free diet and see if CD symptoms improved (even if not diagnosed with CD); of these, 22 (4.7%) also said that they may consider restarting a gluten diet and having a biopsy if a gluten-free diet did not work:

> *I could try the gluten-free diet and if my symptoms improve I would continue, if it makes no difference I may go back to eating gluten and then opt for a biopsy or other tests.*

Thirty-five (7.5%) respondents have said that whether or not they live with another person who has CD would affect their gluten-free diet adherence, and 48 (10.3%) expressed a negative opinion on following a gluten-free diet or see a gluten-free diet as a big commitment. More of those with a CD diagnosis expressed negativity towards a gluten-free diet than those without CD [CD, $n = 33$ (13.5%); no CD, $n = 15$ (6.7%)]:

> *I have 30 years on a [gluten-free diet], I know what it is like. You would want to be sure before changing your diet for good. It isn't much fun, long term.*

Chapter 8 Assessment of cost-effectiveness of diagnostic strategies

This chapter describes the decision tree and Markov modelling to estimate the cost-effectiveness of screening strategies for CD among men, women and children. This builds substantially on previous chapters. Individual diagnostic indicators from *Chapter 3* and combinations of diagnostic indicators from the prediction model in *Chapter 4* are investigated in combination with serological and genetic tests. Serological test accuracies come from *Chapter 5* and genetic test accuracy comes from *Chapter 6*. Results of the patient survey in *Chapter 7* inform the key assumptions of the model. The objectives of this analysis were to determine the following:

- the most cost-effective combination of sensitivity and specificity for a pre-test probability above which all patients should be screened
- the most cost-effective screening strategy.

Results were based on a lifetime time horizon and take a UK NHS perspective.

Screening strategies to investigate

To examine the most cost-effective combination of sensitivity and specificity for a diagnostic indicator (or combinations of diagnostic indicators) above which all patients should be screened, we considered a theoretical selection of combinations of diagnostic indicator sensitivities and specificities. These were every 10% increment > 50% for both parameters. A desired threshold of 90% post-test probability before initiating a gluten-free diet was adopted following the results of the patient survey, described in *Chapter 7*. This survey found that those without symptoms required a median post-test probability of 90% (IQR 66–99%) before committing to a gluten-free diet, whereas those with symptoms required a median post-test probability of 66% (IQR 33–90%). We chose the maximum of these two as the desired level of certainty from testing strategies.

For each combination of sensitivity and specificity of diagnostic indicators, we modelled the following screening strategies:

- serological testing (IgA tTG, IgA EMA, IgA tTG plus IgA EMA) with a confirmatory biopsy for those with a post-test probability of < 90%
- a combination of serological testing with genetic testing (HLA before or after each serological test or test combination) with a confirmatory biopsy for those with a post-test probability of < 90%.

We also investigated 'strategies of interest', identified as the sensitivity and specificity of diagnostic indicator strategies described in *Chapters 3* and *4*, which are pre-test probabilities above which to test for CD. These diagnostic indicator strategies were combined with the serological and genetic testing strategies identified as cost-effective in the previous step.

We compared the strategies with one in which nobody is screened. No screening is equivalent to standard-of-care opportunistic screening, as the model allows diagnosis independently of screening strategies.

The analyses were stratified into adult men, adult women and children. Adults were assumed to be initially 18 years of age. The mean age of children was assumed to be 10 years in accordance with CPRD data on people with CD aged < 18 years. The proportion of children who were female was assumed to be 50%.

Methods for cost-effectiveness analysis

Our model development was based on a review of previously published models; the results of the diagnostic indicator review (see *Chapter 3*) and CPRD analysis of diagnostic indicators for CD (see *Chapter 4*), which identified important patient characteristics for modelling; the results of the meta-analysis on serological and genetic test accuracies (see *Chapters 5* and *6*), which identified tests to model; the survey of patient opinion (see *Chapter 7*); and discussion with our clinical and patient advisers.

Review of previous cost-effectiveness models

To identify important elements of CD to model, and potentially identify existing models we could adapt, we reviewed previously published models as a first step in our method of model development.

Search strategy

We searched Embase and combined terms for CD with an economic model filter. This identified 390 papers, which were screened independently by two reviewers. We identified 13 papers as relevant. Any studies that contained any type of decision-analysis model for CD were eligible for inclusion. We excluded economic evaluations not based on cost-effectiveness models. The full search strategy is provided in *Appendix 24*.

Summary of identified models

Of the 13 economic models identified, seven were decision trees, four were Markov models and two were decision trees followed by Markov models. Only the NICE 2015 model was in a UK setting.[193] Of the others, one was set in the Netherlands[194] and the rest were based in the USA.[195–203,206,207] The studies are discussed in chronological order and details are shown in *Appendix 25*, *Table 62*.

Harewood and Murray[195] developed a decision tree to compare the costs of different screening strategies for the detection of CD. This study found screening with EMA to be the less costly than both screening with GAs and small bowel biopsy in a low- to medium-risk population. We note, however, that GAs are not recommended by NICE because of their low accuracy.[193] Mein and Ladabaum[196] used a decision tree to explore the cost-effectiveness of different screening strategies for CD in patients with IBS symptoms. They concluded that testing for tTG to diagnose CD in patients with a diagnosis of IBS is cost-effective at thresholds of US$50,000 (assuming a prevalence of CD in IBS patients of 2%) and US$100,000 (assuming a prevalence of CD in IBS patients of 1.1%) per QALY gained. Spiegel *et al.*[197] built a decision tree followed by a Markov model to evaluate different screening strategies for CD in IBS patients with predominant diarrhoea symptoms. They found that serological testing for CD resulted in 51.6% of the patients achieving symptomatic improvement at 10 years (at an average cost of US$4100 per patient treated). Starting IBS therapy without testing for CD resulted in 50.9% of the population achieving symptomatic improvement (at an average cost of US$4023 per patient treated). The incremental cost-effectiveness ratio (ICER) of CD testing, compared with IBS treatment alone, was US$11,000 to achieve one additional symptomatic improvement. Testing for CD was, therefore, considered cost-effective.

Shamir *et al.*[198] developed a lifetime Markov model to conduct a cost-effectiveness analysis comparing seven screening strategies for CD in the adult population. The ICER was US$44,941 per life-year gained for screening, compared with no screening, using an IgA EMA testing strategy. All remaining six strategies were dominated and thus excluded. Swigonski *et al.*[199] used a decision tree to evaluate the cost-effectiveness of screening for CD among asymptomatic children with Down syndrome to prevent lymphoma. They found that screening for CD among children with Down syndrome is more costly and less effective than not screening, and decreases quality of life.

Dorn and Matchar[200] evaluated the cost-effectiveness of five strategies for diagnosing CD. The IgA tTG-alone strategy was the least costly (US$22 per person), but also the least accurate. IgA tTG then

HLA then oesophagogastroduodenoscopy (OGD) cost US$2233 per additional correctly diagnosed case. IgA tTG followed by further IgA testing and then OGD biopsy was US$32,605 per additional correctly diagnosed case. OGD with biopsy alone had an ICER of > US$1M. Chang and Green[201] developed a decision tree to evaluate the cost of genetic testing before serological screening among relatives of people with CD. The cost of initial screening with IgA tTG of relatives was US$434 per person. Genetic screening before serological screening of relatives was more costly, at US$750 per person. In terms of cost per correct diagnosis of CD, it would cost US$2668 per case in the initial IgA tTG branch, and US$4422 per case in the HLA branch. The incremental cost per additional case of CD diagnosed would be approximately US$449,000 for genetic testing when compared with IgA tTG alone.

Hershcovici *et al.*[202] developed a Markov model to estimate whether or not mass screening using serological tests followed by biopsy is cost-effective compared with no screening. The ICER of screening compared with no screening was US$48,960 per QALY gained. However, at a US$50,000 threshold, the probability of being cost-effective was 60%. Mohseninejad *et al.*[194] conducted a cost-effectiveness analysis of targeted screening for CD among IBS patients and compared serological screening with no screening. They concluded that screening patients with confirmed IBS symptoms for CD is cost-effective (ICER of €6200).

Park *et al.*[203] developed a Markov model to determine the cost-effectiveness of universal serological screening to prevent non-traumatic hip and vertebral fractures among patients with CD. They found that universal screening, compared with standard care (i.e. screening only symptomatic or at-risk patients), is not cost-effective. Standard care was associated with lower costs (US$8472) and more QALYs (25.515). Yang *et al.*[206] conducted a cost-effectiveness analysis of routine duodenal biopsy for CD during endoscopy for gastro-oesophageal reflux, compared with no biopsy, using a lifetime decision tree. They found that performing a biopsy to detect CD among patients with gastro-oesophageal reflux disease is not cost-effective (ICER of US$121,875 per QALY gained). Broide *et al.*[207] built a Markov model to determine the cost-effectiveness of routine duodenal biopsy to detect CD among patients with IDA. The intervention (biopsy during an OGD in all patients with IDA, irrespective of serological test results) resulted in 19.888 QALYs gained and an average cost of US$218.10, dominating the comparator (i.e. performing biopsy only in patients with a positive serological test), which had a gain of 19.887 QALYs at an average cost of US$234.17.

In 2015, NICE conducted a cost-effectiveness analysis using a decision tree followed by a Markov model to estimate which serological test is the most appropriate to diagnose CD among both children and adults.[193] For adults, the most effective strategy was the most sensitive: considering people serologically positive if they are positive on either IgA tTG or IgA EMA (17.6004 total QALYs). However, the ICER was £173,484 per QALY gained. The incremental analysis suggested that most benefits could be achieved at a lower cost by a strategy that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive. All other strategies were strongly dominated. For children, the most effective strategy was IgA tTG plus IgA EMA plus HLA (a combination of serological tests for IgA tTG and IgA EMA and *HLA-DQ2/-DQ8* genotyping), with a total QALY gain of 21.3823. The ICER of this strategy was £33,800 per QALY gained, compared with the next cheapest non-dominated option. NICE also conducted a health economic evaluation of active case-finding strategies. It found that screening first-degree relatives of people with CD was cost-effective among adults and children, that screening people with type 1 diabetes was cost-effective among adults and potentially cost-effective among children, and that screening those with autoimmune thyroid disease was not cost-effective among adults or children.

Implications for cost-effectiveness modelling in coeliac disease

A Markov model, rather than a decision tree, is most appropriate for modelling a long-term health-care condition such as CD, as comorbidities, including non-Hodgkin lymphoma (NHL), may not develop for a long time after the initial screening.[208,209] A decision tree is an appropriate structure to model the initial set of testing strategies, but must be combined with a Markov model to capture long-term impacts.[210,211]

Only three of the Markov models considered mass screening, rather than screening focused on patients with fractures, IDA, IBS or Down syndrome. Shamir *et al.*[198] used states for CD undiagnosed, CD diagnosed on gluten-free diet and CD diagnosed but off gluten-free diet, while Hershcovici *et al.*[202] considered states related to whether patients were diagnosed, undiagnosed, adhered to a gluten-free diet, had IDA or had IBS. The NICE 2015 Markov model was the only model in the UK setting and its Markov model included states only for health conditions with a strong impact on costs and effects.[193] They used CD on gluten-free diet and CD not on gluten-free diet as primary states, with different levels of IDA, IBS and other symptoms in these states. They additionally included subfertility, osteoporosis, NHL and other cancers as health states. As the NICE model considered more events and had a richer evidence base than Shamir *et al.*[198] or Hershcovici *et al.*,[202] it was taken as the starting point for our model.

Model structure

As explained previously, we adopted a decision tree followed by a Markov model, as this can fully describe testing strategies and model long-term consequences of CD, and we largely follow the evidence-based model of NICE 2015.[193,211] Initial prevalence of CD is determined by a selected pre-test probability of CD, representing the target population for screening, and this drives the maximum number of true positives (i.e. diagnosed CD) that our testing strategy can identify. The decision tree captures the sensitivity and specificity of serological and genetic tests from *Chapters 5* and *6*, respectively, along with costs and impacts on health of these tests and the confirmatory biopsy. The Markov model captures the costs and health impacts of having diagnosed or undiagnosed CD, and thus measures the benefit of initially detecting CD with the decision tree. Modifications were made to the Markov model used by NICE following discussion with our clinical and patient advisers, and the results of our CPRD analysis of risk factors for CD (see *Chapter 4*); these are described in more in *Structure of the Markov model*.

Structure of the decision tree

The decision tree in which various serological and genetic test combinations are included is illustrated in *Figure 12*. Patients enter the tree either with CD (CD+) or without CD (CD–) and then follow one of three branches representing the three strategies: screening by serological testing, screening by serological and genetic testing, or no screening (representing standard of care). If a strategy combines serological and genetic testing, the second test is used only if post-test probability following the first was < 90% (see *Chapter 7*). In each case in which a person is tested, a confirmatory biopsy is used only if the post-test probability of having CD is < 90%. This does not apply to the combination of IgA tTG and IgA EMA, which were based on the results of joint testing, reported in *Chapter 5*. The model assumes that biopsy is perfectly accurate.

At the end of the decision tree, patients have either a positive or a negative result for CD or remain undiagnosed if they followed the no-screening strategy or had a false-negative test. If they are diagnosed with CD through the testing process, they would be advised to follow a gluten-free diet. It is assumed that, beyond the initial costs and disutility associated with testing, patients without CD who are tested will not have different costs or health outcomes from non-CD patients who were not screened. As a result, we model only the long-term consequences of patients who have diagnosed or undiagnosed CD. Costs and effects associated with false-positive CD patients are scaled by the ratio of false positives to true positives and false negatives (i.e. the number of CD patients who enter the cohort Markov model), so they are on the same scale as the diagnosed/undiagnosed CD cohort.

Structure of the Markov model

The decision tree is followed by a lifetime time-inhomogeneous discrete-time Markov model.[208,212] In this model, health states are assumed to be mutually exclusive. In other words, a patient can be in only one health state at a time. Costs and utilities are assigned to each health state, and are accrued for each year spent in that state. As in the NICE 2015 model,[193] our model has annual cycles and a lifetime horizon.

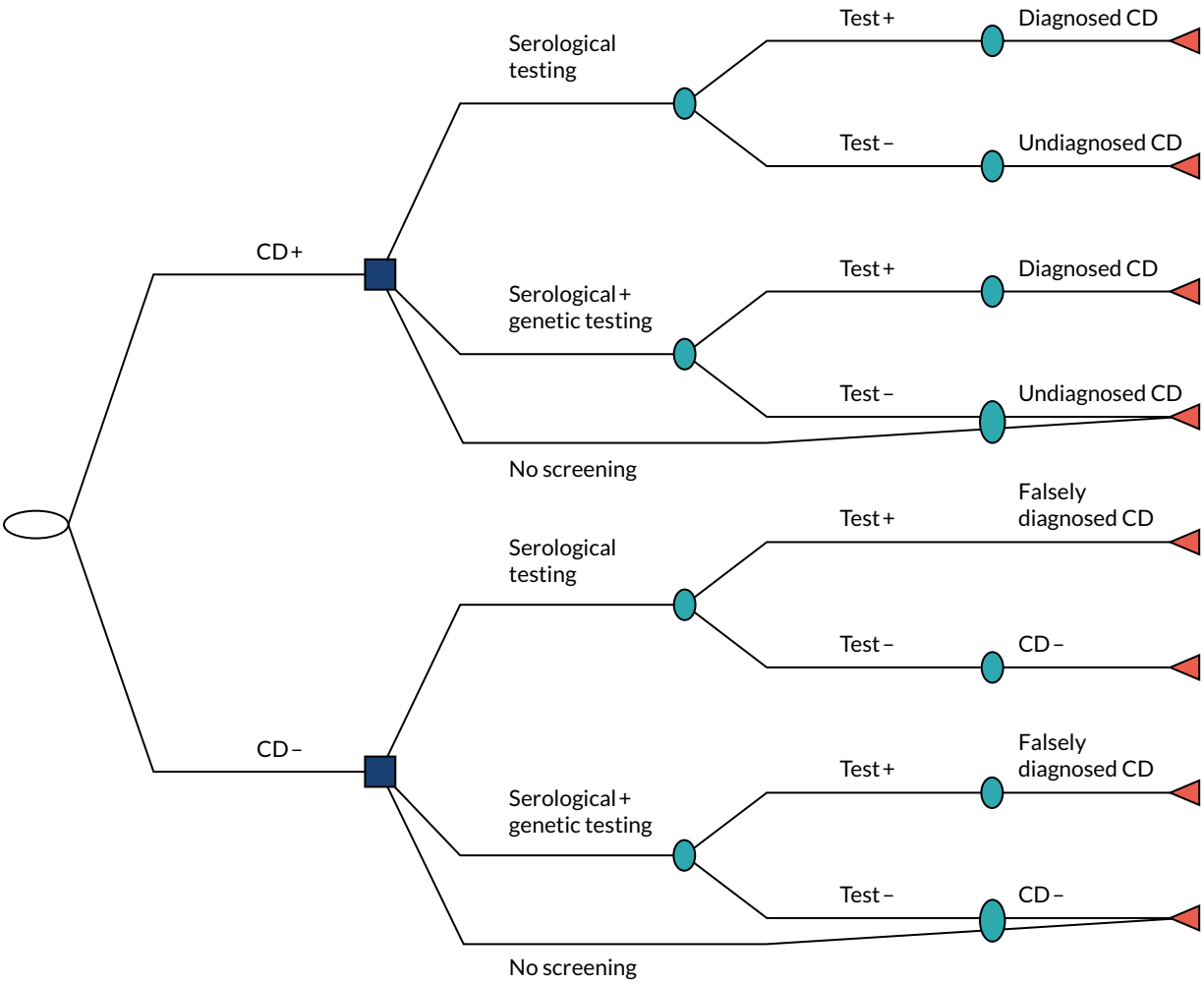

FIGURE 12 Decision tree representing serological and genetic testing among patients with suspected CD. A test is judged to be positive if a patient's post-test probability of having CD is > 90%; confirmatory biopsy is applied to all strategies if the post-test probability is below this threshold.

Following the NICE model, complications from biopsy are not modelled, thus implicitly assuming that there is no elevated risk of major complications or death from biopsy, although a small disutility is included to represent the procedure and waiting time for diagnosis, during which an undiagnosed CD patient is less likely to be on a gluten-free diet. This assumption is supported by a 2018 study[213] that looked at 13,233 patients undergoing outpatient OGD with biopsy over 5 years in the USA. The authors concluded that no patient was admitted because of complications that could be ascribed to conscious sedation, upper GI endoscopic access or mucosal biopsy and that these data confirm that OGD biopsy is safe.[213]

Unlike the NICE 2015 model,[193] our model does not distinguish between people with diagnosed CD following a gluten-free diet and people diagnosed with CD not following a gluten-free diet. We instead modelled CD patients as being diagnosed or undiagnosed, with different rates of complications in these states due to different levels of adherence to a gluten-free diet. This modelling choice is because of methodological challenges associated with assessing dietary adherence and a lack of reliable data on the health impacts of following a gluten-free diet or not. Reported gluten-free diet adherence rates vary substantially depending on how adherence is measured and the population studied.[214] Adherence to a gluten-free diet is affected by age at diagnosis, type and severity of symptoms, quality of counselling, mental health, local or societal support levels, and the cost and availability of gluten-free foods.[215] Biopsy is the gold standard when assessing adherence, but the procedure is invasive and costly. For this reason, various other methods are used including validated and non-validated questionnaires, serology, faecal or urine tests, dietitian's assessment, interviews

and patient-reported adherence.[215] Identifying and assigning an average adherence rate to a cohort of individuals is therefore very difficult. Even if this were possible, studies informing the risk of developing complications among those on a gluten-free diet, compared with those who are not, are based on cohorts of people with unknown, and presumably mixed, adherence.

A further distinction from the NICE model[193] is that we do not include subfertility as a separate state. Our CPRD analysis found that the prevalence of subfertility among women is the same regardless of CD status; this is supported by a growing literature that there is no association between CD and subfertility.[216–219]

Iron-deficiency anaemia was identified as important in our CPRD analysis, but, in line with NICE, was not modelled as a separate state as our patient and clinical advice was that costs were mostly for over-the-counter medications, and therefore not included from an NHS perspective. The impact of IDA was also captured in utility values in diagnosed and undiagnosed states, aligned with our modelling of the efficacy of a gluten-free diet, as major CD utility studies included large proportions of people with IDA.

Further risk factors of CD identified by the diagnostic indicator review (see *Chapter 3*) and the CPRD analysis (see *Chapter 4*) (1) are captured as general symptoms (e.g. fatigue, GI symptoms, IBS, mood disorders), (2) cannot be affected by a gluten-free diet and are thus unaffected by diagnosis (e.g. Down syndrome or having a first-degree relative with CD) or (3) are either rare or not plausibly caused by CD (e.g. thyroid disorders, Turner syndrome, type 1 diabetes).

Our final Markov model is illustrated in *Figure 13*.

The initial distribution of patients between diagnosed and undiagnosed CD states is determined by the decision tree. People can transition to death from any state in the model. Patients have an annual probability of transitioning from no complications to health states representing osteoporosis, NHL and death. Patients can also be in any of these health states at diagnosis. As in the NICE model,[193] and to avoid modelling multiple comorbidities on which CPRD evidence is limited, patients who develop osteoporosis can transition to NHL or death only, and no distinction is made between NHL patients

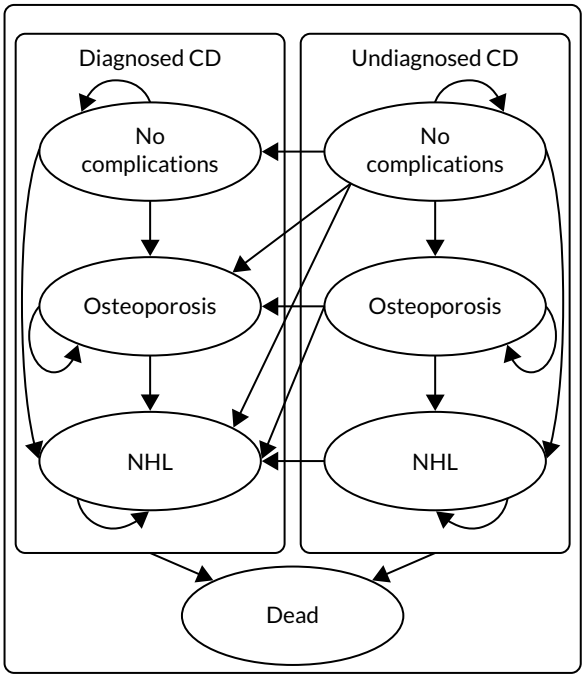

FIGURE 13 Markov model structure.

with and NHL patients without prior osteoporosis. Patients who develop NHL are assumed to stay in this health state until death (i.e. they do not return to the less severe osteoporosis state). Patients with undiagnosed CD transition through the health states and can be diagnosed at any point, with a proportion receiving biopsy.

Input parameters

In this section we describe the parameters of the decision tree and Markov model. These are informed by the DTA meta-analysis (see *Chapters 5* and *6*), the literature review of coeliac screening cost-effectiveness models, UK CPRD analyses, estimates used in the NICE 2015 model[193] or targeted literature searches. A summary of all parameters with evidence sources is shown in *Table 18*.

Prevalence of osteoporosis, non-Hodgkin lymphoma and iron-deficiency anaemia in a population with coeliac disease

The prevalence rates of NHL, osteoporosis and IDA were estimated using the CPRD Aurum data of patients with a CD diagnosis, linked to HES, and these rates were assumed to be age and gender dependent. Records of complications were identified in HES and the CPRD using the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), and Aurum medical codes (full details of the analysis and results are in tables S12–S16 in *Report Supplementary Material 1*). The initial proportions of people with each complication among newly diagnosed and undiagnosed CD patients in the Markov model are assumed to follow these prevalences. It is a limitation that CPRD data cannot generate prevalence rates of NHL, osteoporosis and IDA in those with undiagnosed CD; however, rates of developing each of these complications are modelled to be different from those in patients with a CD diagnosis (see *Risk of developing osteoporosis, iron-deficiency anaemia and non-Hodgkin lymphoma*). Patients without these complications begin in the no-complications state. IDA is modelled independently of NHL and osteoporosis, so an independent beta distribution is used to present the initial probability of having IDA. Although NHL and osteoporosis are separate states in the Markov model, the prevalence estimates are not mutually exclusive. The prevalence of NHL is low (< 2%), so overlap with osteoporosis is negligible and each prevalence is modelled by an independent beta distribution. *Appendix 26*, *Table 63*, includes estimates of the prevalence of each of these complications in a mixed-gender cohort of > 48,046 people with a CD diagnosis recorded in CPRD Aurum. This is stratified into men and women in *Appendix 26*, *Tables 64* and *65*, respectively. The adult men and adult women analyses use the stratified estimates whereas the children analyses use the mixed-gender estimates.

Percentage receiving biopsy

The percentage of patients with a delayed diagnosis assumed to require a confirmatory biopsy is 70%, based on clinical advice and in accordance with recent research indicating high diagnostic accuracy of tests alone.[70,89,220,221] This percentage is varied within a 95% credible interval (CrI) of 60% to 80%. The 60% lower bound is based on the findings of a retrospective study of 270 adult patients.[89] This study found that, at an IgA tTG antibody cut-off point of > 45 U/ml, the PPV for CD was 100%, and that 40% of cases were above this cut-off point.

Diagnostic accuracy of tests

The diagnostic accuracy parameters for IgA tTG, IgA EMA and IgA tTG plus IgA EMA were informed by the DTA meta-analysis (see *Chapter 5*). The diagnostic accuracy of HLA tests was informed by the genetic test accuracy meta-analysis (see *Chapter 6*). In the serological followed by HLA testing and HLA followed by serological testing combinations, the second test was used only with patients whose post-(first)-test probability was < 90%, aligning with the patient survey result that this was a threshold above which they would be willing to go on a gluten-free diet (see *Chapter 7*). Estimates of the test accuracy of serological tests were assumed to be independent of HLA test accuracy. All tests are followed by a confirmatory biopsy among those with a post-test probability that is still < 90%.

Costs

The model includes costs associated with diagnostic tests, biopsy, annual health-care resource use costs among diagnosed CD patients, and annual costs of osteoporosis and NHL. A price year of 2018/19 was assumed, aligning with NHS reference costs.[222] The cost of IgA tTG, IgA EMA and HLA tests were sourced from correspondence with hospitals and testing centres affiliated with the research team. The cost of biopsy was informed by NHS reference costs.

Along with test and biopsy costs, to get to a diagnosis, patients would also have nurse, GP and/or specialist consultations. Our clinical and patient team advised on the likely pathway to diagnosis. We assumed that a person's first appointment is with either a nurse or a GP, at a cost of £10.85 or £39.23, respectively, with average £25.04, reported by the Personal Social Services Research Unit.[223] This is assumed to be followed by phlebotomy at a cost of £4, following NHS reference costs 2018/19, and then by a further GP appointment.[222] Following that, we assumed patients have, on average, one gastroenterology outpatient appointment costing £141 and two dietitian appointments at a cost of £85 each before diagnosis.[223] This gives a total cost of £379.27 (£25.04 + £4 + £39.23 + £141 + £170) for a patient to reach diagnosis. This cost is applied to both true positives and false positives in the model.

Annual health-care resource use costs for patients with CD were based on analysis of CPRD data, which updated the 2012 analysis of Violato *et al.*;[50] full details can be found in *Report Supplementary Material 1*, chapter 8. Following this earlier analysis, we quantified the volume of health-care resources in terms of primary care consultations, tests, referrals to outpatient hospital care and prescriptions used by individuals diagnosed with CD up to 10 years before and after diagnosis in a UK primary care setting. The volumes of resources, along with unit costs, have been used to estimate overall medical costs associated with a true-positive or false-negative diagnosis. A limitation of this analysis is that referrals to gastroenterology are likely to include only adult referrals, as children referred to gastroenterology are normally recorded under paediatrics. The unit costs used and a breakdown of costs are provided in tables S17 and S18 (see *Report Supplementary Material 1*).

The model assumed that patients falsely diagnosed with CD would follow a gluten-free diet for a limited time before stopping. Although such patients are not included in the Markov model, we count this short-term impact in the total costs (and total effects). Following input from clinicians and patient advisors on the likely time taken to decide that the diet is not of benefit, we assumed that this time would be 1 year with a log-normal distribution to reflect skew towards longer durations. The only additional cost incurred by people with a false-positive diagnosis of CD was the cost of non-NHS-reimbursed gluten-free products. We assumed that no other costs are incurred by people with a true-negative diagnosis.

The cost associated with NHL was based on a study by Wang *et al.*,[224] which followed all patients newly diagnosed with diffuse large B-cell lymphoma in the UK's population-based Haematological Malignancy Research Network from 2007 to 2013 ($n = 271$). Mapped treatment pathways, alongside cost information derived from the National Tariff 2013/14,[225] were incorporated into a patient-level simulation model to reflect heterogeneities in patient characteristics and treatment options. As treatment for NHL is usually complete within 5 years, most costs were estimated to fall within 5 years. The mean cost per patient was £18,096 (95% CI £18,078 to £18,114) over a 5-year time horizon and £18,396 (95% CI £18,377 to £18,415) over a lifetime time horizon. Using lifetime costs is problematic for a cohort Markov model as some patients may develop NHL at an advanced age and not have many additional years to incur costs. However, the NHL model factors in different survival times when estimating the treatment costs, so patients would incur less cost if they died within a shorter time. We therefore assumed a one-off cost of £18,396 (95% CI £18,377 to £18,415) with a log-normal distribution, relating to the lifetime cost estimated by Wang *et al.*[224]

For the cost associated with osteoporosis, a similar approach to that of the NICE model[193] was taken, with the cost being equal to the annual probability of hip, vertebral and wrist fracture multiplied by the cost of each type of fracture. Probabilities were estimated from Curtis *et al.*,[226] who used CPRD data to

look at trends in fracture rates in the UK over a 24-year period from 1988 to 2012.[226] The rates of hip, clinical vertebral and carpus (wrist) fractures found among those aged 18–49 and ≥ 50 years are shown in *Appendix 27*, *Table 66*.

For the cost associated with hip fractures, Leal *et al.*[227] estimated hospital costs up to 2 years post fracture using a cohort of 33,152 patients aged > 60 years admitted with a hip fracture in a UK region between 2003 and 2013 who were identified from hospital records and followed until death or administrative censoring. The mean censor-adjusted 2-year hospital cost after index hip fracture was £16,302 (95% CI £16,097 to £16,515).[227] For costs associated with vertebral and wrist fractures, we used estimates from Dolan and Torgerson,[228] who estimated the cost per annum to be £468 per wrist fracture and £479 per vertebral fracture. These were based on health and social care costs of fractures among women aged ≥ 50 years in the UK using a variety of data sources including published estimates, a survey of resource use among fracture patients before and after hip fracture and a case–control study using the General Practice Research Database. All costs are inflated to 2021 prices using the Composite Price Index published by the Office for National Statistics.[229] The overall assumed annual cost of osteoporosis is shown in *Appendix 27*, *Table 67*. Uncertainty was included by fitting gamma distributions to the cost of hip, vertebral and wrist fractures, with the SE set to one-tenth of the mean.[212]

The cost of IDA is only that related to over-the-counter iron tablets, which incur no NHS cost.

Utilities

The model includes health-state utility values associated with undiagnosed CD and diagnosed CD, and disutilities associated with osteoporosis and NHL. As explained, we assume that some proportion of diagnosed CD patients will adhere to a gluten-free diet, so utilities for diagnosed CD should represent this mixed population. We assumed that the health-state utilities for osteoporosis and NHL are the same as for the general (i.e. not CD-specific) population. The model also includes disutilities associated with the biopsy procedure, with the waiting time associated with a biopsy and with a lifetime false-positive diagnosis.

Quality-adjusted life-year norms for the UK are used to reflect background age-specific quality of life, which decreases naturally with age. All state QALYs are multiplied by their norms to reflect this age reduction. The values used, sourced from Janssen and Szende,[230] are shown in *Appendix 28*, *Table 68*.

The utility values for undiagnosed CD and diagnosed CD were sourced from Violato and Gray.[231] The values are based on 1584 EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaires retrospectively completed by people with CD in the UK. Participants rated their health using the validated questionnaire before and after their diagnosis. Not all of the diagnosed cohort adhered perfectly to a gluten-free diet, with 90.8% reporting adherence all of the time, 8.3% most of the time and 0.9% some/little/none of the time. The estimated utility values for diagnosed CD and undiagnosed CD were 0.65 (95% CI 0.63 to 0.67) and 0.85 (95% CI 0.84 to 0.86), respectively, in the total sample. In the subgroup aged < 18 years, the values were 0.57 (95% CI 0.51 to 0.64) for undiagnosed CD and 0.88 (95% CI 0.85 to 0.92) for diagnosed CD on gluten-free diet. An alternative source for utility in diagnosed and undiagnosed CD was identified in Casellas *et al.*,[232] who carried out a prospective study of 163 CD patients on a gluten-free diet and 177 newly diagnosed CD patients on a normal diet from seven hospitals in different areas of Spain, with all completing the EuroQol-5 Dimensions (EQ-5D). A similar pattern was found to our selected source, with the median EQ-5D value being 0.93 (95% CI 0.85 to 1.0) among gluten-free diet patients and 0.72 (95% CI 0.58 to 1.0) in the normal diet group.

For osteoporosis, a similar approach is taken as with costs, with total disutility being equal to the annual probability of hip, vertebral and wrist fractures multiplied by the disutility associated with each type of fracture. The results are presented in *Appendix 28*, *Table 69*. These disutilities are estimated from the Si *et al.*[233] study, which was a systematic review and meta-analysis of 62 studies reporting

utility-based quality of life for osteoporosis-related conditions. Most of the studies used EQ-5D health-state utility values, followed by a visual analogue scale. Si *et al.*[233] calculated utilities for the first year after hip, vertebral and wrist fractures as 0.59 (95% CI 0.54 to 0.65), 0.55 (95% CI 0.50 to 0.60) and 0.78 (95% CI 0.72 to 0.84), respectively. These utilities are subtracted from the UK population norm of 0.817 for the group aged 55–64 years. Uncertainty was modelled by moment-matching beta distributions to the hip, vertebral and wrist fracture disutilities, with the SE for each set to one-tenth of their means.[212]

The utility associated with NHL is based on an observational cross-sectional comparative study carried out by Fargier *et al.*[234] in three French teaching hospitals. In this study, 73 patients with follicular lymphoma were receiving either subcutaneous or intravenous rituximab maintenance monotherapy (73% as first-line treatment, 21% as second-line treatment and 6% as third-line treatment). Health-related quality of life was evaluated using the French version of the self-administered EQ-5D-3L questionnaire. The aim was to compare the impact of using subcutaneous rituximab with that of using intravenous rituximab as maintenance therapy. The mean EQ-5D score was 0.8 for intravenous rituximab and 0.7 for subcutaneous rituximab.[234] The average of these two values is subtracted from the French EQ-5D population norm for people in the 55–64 years age group (0.836[230]), giving a disutility of 0.086. The upper and lower bounds, of 0.8 (disutility 0.036) and 0.7 (disutility 0.136) respectively, are used to represent uncertainty in this parameter using a uniform distribution.

The disutility associated with a biopsy in adults is assumed to be equal to 1 quality-adjusted life-day. This is the same assumption made in the NICE model[193] and aims to account for any anxiety associated with the biopsy as well as potential side effects. For children, the loss of 2 quality-adjusted life-days is assumed because of the need for general anaesthetic. The disutility associated with waiting for a biopsy is assumed to be equal to the difference between the utility of being diagnosed with CD and following a gluten-free diet and the utility of having undiagnosed CD. This disutility is assumed to last for 6 weeks in accordance with average waiting times for a biopsy.

In line with the NICE model,[193] we assume an annual disutility for patients falsely diagnosed with CD of 0.009. This was based on an estimated change in social function score on the Short Form questionnaire-36 items of −8.3 (SE 3.83) and a mapping for this score to utility scale of 0.0011 (SE 0.0002). We modelled these uncertain factors with normal distributions and the mean of their product was −0.009 (SE 0.004). Note that we assume that any disutility from a gluten-free diet in the true CD population is captured by the Violato and Gray[138] 2019 survey.

For IDA, we assume that disutility is already captured in the utility values for undiagnosed CD and diagnosed CD sourced from Violato and Gray,[138] as they reported that 64.8% of their population had anaemia prior to diagnosis and 14.5% after.

Probability of late detection of coeliac disease after false-negative diagnosis

All patients in the undiagnosed CD state have an annual probability of transitioning to the diagnosed CD state. Violato and Gray[138] asked patients about the duration of their symptoms prior to diagnosis and found that the average duration was 12.8 years (SD 15.3 years), based on 1584 completed questionnaires. The average duration across the sample aged '< 18' was shorter, at 3.3 years (SD 3.7 years). As our adult cohort begins at age 18 years, we need the time to diagnosis only as an adult. We use these figures to calculate this average duration in patients aged > 18 years of 10.9 [(12.8 − 3.3) × proportion aged < 18 years) × (proportion aged > 18 years ÷ 1584)]. Although our children cohort begins age 10 years, it was not reported what proportion of patients were under the age of 10 years, so the '< 18' years figure had to be used. We model the average duration as a log-normal distribution moment matched to the reported mean and SE calculated using SD and sample size. Assuming a constant rate, λ, of diagnosis (i.e. an exponential survival model), the rate is the inverse of the sampled duration. This is used to calculate an annual probability of diagnosis by year of $1 - e^{-\lambda t}$.

Risk of developing osteoporosis, iron-deficiency anaemia and non-Hodgkin lymphoma

Patients who are diagnosed have a lower risk of developing long-term complications than patients who are undiagnosed, owing to the greater likelihood of following a gluten-free diet and receiving improved care and medical advice. To inform the risk of developing long-term complications, we use rates in non-CD patients estimated using CPRD data (full details are in *Report Supplementary Material 1*, chapter 8), differences in rates between this general population and patients who are diagnosed with CD, and differences in rates between the general population and those with undiagnosed CD. Evidence on these differences primarily comes from the NICE 2015 model.[193] In each case, the literature was searched for more recent or higher-quality studies, but none was identified.

The NICE model[193] based the risk of developing osteoporosis when following a gluten-free diet on Swedish data from a study by Ludvigsson *et al.*,[235] which comprised > 13,000 people diagnosed with CD and compared this group with a matched control group. This study did not distinguish between patients diagnosed with CD and on a gluten-free diet and those diagnosed but not on a gluten-free diet, so it represents our merged diagnosed CD state. The study reported an odds ratio of fractures of any type in the diagnosed CD population, compared with the controls, of 1.40 (95% CI 1.30 to 1.50). The NICE model[193] based the risk of developing osteoporosis when not following a gluten-free diet on a study by Godfrey *et al.*,[236] who tested blood samples for CD and compared the medical records of 129 US people with not diagnosed with CD, but with positive coeliac serology, with those of seronegative individuals. They found an odds ratio for developing osteoporosis of 2.59 (95% CI 1.32 to 5.09) in the undiagnosed CD group, compared with those without CD, and this is the ratio we used in our model. This finding contradicts that of Ludvigsson *et al.*,[235] who found no association between date of diagnosis, used as a proxy for initiating gluten-free diet, and risk of osteoporosis. However, Ludvigsson *et al.*[235] did not have data on adherence to gluten-free diet in either diagnosed or undiagnosed states, and so is confounded in comparison with Godfrey *et al.*[236]

The NICE model[193] based the probability of patients developing NHL from CD when not on a gluten-free diet on a study of 1968 previously undiagnosed patients who were subsequently diagnosed with CD at 20 Italian gastroenterology referral centres.[237] The incidence ratio of NHL in the population with undiagnosed CD compared with the general population was found to be 4.7 (95% CI 2.9 to 7.3). The incidence ratio of NHL in the population with diagnosed CD (3.28, 95% CI 1.49 to 6.28), relative to the general population, was based on an analysis of a cohort of patients with diagnosed CD from a linked statistical database of hospital and mortality data in an area in southern England.[238]

Normal distributions were used to model the log-odds ratios and incidence ratios of osteoporosis and NHL, respectively (i.e. log-normal distributions). We added these log ratios to the log of rates of developing long-term conditions among control (i.e. non-CD) patients from our CPRD analysis (*Table 16*). Rates were calculated from the number of outcome events divided by the person-time at risk stratified by decile of age at index date (date of CD diagnosis in matched case) for osteoporosis and IDA. For NHL we grouped patients into those aged < 18 years and those aged ≥ 18 years because of limited sample size. Time at risk was calculated from a patient's index date to date of outcome event, date of death or the end date of HES coverage. The rates were used to calculate the annual probabilities of developing the conditions, with uncertainty based on a log-normal distribution of the rates mapped to a log scale, consistent with the ratios for osteoporosis and NHL.

Assuming that events occur at a constant rate r per unit of time t, the probability that an event will occur during time t is given by $p = 1 - e^{rt}$, equivalent to an exponential survival distribution.[239]

Mortality

Mortality in the model is assumed to be equal to general population mortality, with excess mortality assigned to those patients who develop NHL or osteoporosis. Mortality in the general population came from the 2019 Office for National Statistics life tables.[240]

TABLE 16 Age-stratified rates per 1000 (95% CI) among non-CD controls from CPRD analysis

	Rate (95% CI)		
Age group (years)	Mixed gender	Men	Women
NHL			
< 18	0.03 (0.01 to 0.07)	0.02 (0.01 to 0.09)	0.04 (0.01 to 0.12)
≥ 18	0.28 (0.25 to 0.32)	0.30 (0.26 to 0.35)	0.27 (0.23 to 0.32)
Osteoporosis			
0–9	0.02 (0.01 to 0.09)	0.02 (0.00 to 0.15)	0.02 (0.00 to 0.17)
10–19	0.03 (0.01 to 0.10)	0.04 (0.01 to 0.15)	0.03 (0.00 to 0.18)
20–29	0.16 (0.11 to 0.25)	0.10 (0.05 to 0.21)	0.24 (0.14 to 0.41)
30–39	0.42 (0.34 to 0.52)	0.17 (0.10 to 0.27)	0.66 (0.52 to 0.83)
40–49	1.40 (1.20 to 1.50)	0.55 (0.43 to 0.70)	2.20 (1.90 to 2.50)
50–59	3.90 (3.60 to 4.20)	1.20 (1.00 to 1.50)	6.60 (6.10 to 7.10)
60–69	7.50 (7.00 to 7.90)	2.70 (2.30 to 3.10)	12.00 (11.00 to 13.00)
70–79	13.00 (12.00 to 14.00)	4.80 (4.10 to 5.60)	20.00 (19.00 to 22.00)
80–89	21.00 (19.00 to 23.00)	9.60 (7.50 to 12.00)	29.00 (26.00 to 33.00)
90–99	27.00 (19.00 to 38.00)	5.90 (1.50 to 24.00)	36.00 (25.00 to 51.00)

Mortality from NHL is based on data from the Office for National Statistics on adults diagnosed with NHL between 2013 and 2017, which show that 1-year survival is 79.4% (95% CI 79.0% to 79.7%), 5-year survival is 65.6% (95% CI 65.0% to 66.3%) and 10-year survival is 54.7% (95% CI 53.2% to 56.3%).[241] The Markov model cannot allow the probability of NHL mortality to change over time, as patients may enter the NHL state at different times. These estimates are therefore used to calculate a single annual probability capturing average survival.

This synthesis was performed in the Bayesian software OpenBUGS.[242] We first converted observed probabilities to hazards under the assumption of constant hazards, using the following equation:

$$P(t) = e^{-h_t t}. \quad (1)$$

These hazards, h_t, were then converted to a natural log scale (log-hazard y_t) and the upper and lower bounds of the 95% reference range were used to estimate the SE (SE_t) by assuming normality via the central limit theorem. We then treated them as independent observations of a common log-hazard λ:

$$y_t \sim N(\lambda, SE_t), \quad (2)$$

with a vague prior distribution:

$$\lambda \sim N(0, \sigma^2 = 1000). \quad (3)$$

We fit this model in OpenBUGS using two chains, 50,000 burn-in iterations and 10,000 sampling iterations. This gave a posterior mean for λ of −2.092 (SE 0.006378). These are used in the economic model by sampling from a normal distribution with mean −2.092 and SD 0.006378.

This has the limitation that the hazards are changing over time (*Table 17*). This overestimates the hazard in later years and underestimates it in earlier years, but is the closest approximation possible. This is a necessary assumption for a cohort Markov model and, owing to the rarity of NHL, is unlikely to affect the conclusions.

TABLE 17 Office for National Statistics data on the probability of survival following a diagnosis of NHL

Year	Probability survival (95% reference range)	Hazard (95% reference range)	Log-hazard (SE)
1	0.794 (0.79 to 0.797)	0.231 (0.227 to 0.236)	−1.467 (0.00973)
5	0.656 (0.650 to 0.663)	0.084 (0.632 to 0.657)	−2.473 (0.009661)
10	0.547 (0.532 to 0.653)	0.06 (1.08 to 1.154)	−2.808 (0.016893)

For mortality from hip fracture, we used the study by Klop *et al.*,[243] which used CPRD data to examine all-cause and cause-specific mortality post hip fracture among 31,495 patients with a first hip fracture, compared with general population mortality, from 2000 to 2010. The mean age was 74.1 ± 14.8 years for male hip fracture patients and 80.5 ± 10.5 years for female hip fracture patients. During the total study period, the hazard ratio for 1-year all-cause mortality was 3.5 times (95% CI 3.28 to 3.74 times) greater for male hip fracture patients than for control subjects after adjustment for age, comorbidities, medication use and lifestyle factors. For female patients, this risk was 2.4-fold (95% CI 2.31- to 2.50-fold) greater than that of controls.

Table of model inputs

A summary of all input parameters, assumed distributions and evidence sources is provided in *Table 18*.

TABLE 18 Model parameters and data sources

Parameter	Estimate	Distribution	Source
Decision tree and Markov initial probabilities			
Probability of late detection of CD after FN diagnosis	Mean time (years) to diagnosis: • Adults – 10.93 (SD 13.10) • Children – 3.34 (SD 3.71)	Normal	Violato *et al.*[231]
Probability that confirmatory biopsy needed, mean (minimum, maximum)	0.7 (0.6, 0.8)	Uniform	Studies on percentage needing biopsy.[70,89,220,221] The 60% lower bound is based on the findings of a retrospective analysis of 270 adult patients[89]
Proportion with osteoporosis, NHL or IDA at diagnosis	Age dependent (see table S13 in *Report Supplementary Material 1*)	Independent beta for each condition	CPRD age- and gender-stratified prevalence
***Diagnostic accuracy of tests from* Chapters 5 *and* 6**			
Costs			
Unit cost of IgA EMA test	£14.92 (SE £1.87)	Gamma	Personal communication with various laboratories offering CD testing in the UK
Unit cost of IgA tTG test	£10.77 (SE £2.15)	Gamma	Personal communication with various laboratories offering CD testing in the UK
Unit cost of HLA test	£122.34 (SE £24.47)	Gamma	Personal communication with various laboratories offering CD testing in the UK
Endoscopic biopsy, adults: diagnostic endoscopic upper GI tract procedures with biopsy, aged ≥ 19 years	£530	Fixed	NHS reference costs (2018/19)[222] FE21Z

continued

TABLE 18 Model parameters and data sources (*continued*)

Parameter	Estimate	Distribution	Source
Endoscopic biopsy, children: endoscopic or intermediate, upper GI tract procedures, aged between 5 and 18 years	£823	Fixed	NHS reference costs (2018/19)[222] FE23C
Other diagnosis costs (e.g. nurse, GP, gastroenterologist, dietitian appointments)	£379.27 (SE £37.93)	Gamma	NHS reference costs (2018/19),[222] *Unit Costs of Health and Social Care 2020*[223]
Annual health-care resource use costs by diagnosis – TP	• Adults: £757 (SE £5.3)[a] • Children: £452 (SE £20.6)[a]	Gamma	CPRD analysis based on update of Violato *et al.*[50]
Annual health-care resource use costs by diagnosis – FN	• Adults: £421 (SE £3.34)[a] • Children: £248 (SE £4.97)[a]	Gamma	CPRD analysis based on update of Violato *et al.*[50]
Treatment for NHL	£18,396 (95% CI £18,377 to £18,415)	Log-normal	Wang *et al.*[224] One-off lifetime cost of treatment
Osteoporosis	£39.04 (SE £0.27)	Weighted average of gamma distributions (see *Appendix 27, Table 67*)	Curtis *et al.*,[226] Leal *et al.*[227] and Dolan and Torgerson[228]
Anaemia	£0 under NHS (£17.89 if counting over-the-counter expenses)	Fixed	Cost of over-the-counter iron tablets. Costed as 200 mg of ferrous sulfate tablet twice per day; 1000-tablet pack = £17.89, BNF 2020[244]
Utilities			
Diagnosed CD	• Whole population: 0.85 (95% CI 0.84 to 0.86) • Aged < 18 years: 0.88	Beta	Violato *et al* 2019[231]
Undiagnosed CD	• Whole population: 0.65 (95% CI 0.63 to 0.67) • Aged < 18 years: 0.57	Beta	Violato *et al* 2019[231]
Osteoporosis (annual disutility)	0.0008 (SE 0.000067)	Weighted average of beta distributions (see *Appendix 27, Table 69*)	Si *et al.*[233] and Curtis *et al.*[226]
NHL (annual disutility)	0.086 (95% CI 0.036 to 0.136)	Uniform	Fargier *et al.*[234]
Disutility associated with biopsy in adults	−0.003 (95% CI −0.005 to 0)	Triangular	NICE guideline[193]
Disutility associated with biopsy in children	−0.006 (95% CI −0.010 to 0)	Triangular	NICE guideline[193]
Disutility associated with waiting for a biopsy	−0.023 (95% CrI −0.0232 to −0.0227)	Combination	Assumed equal to difference between utility diagnosed CD and utility undiagnosed CD for 6 weeks
Disutility associated with false-positive diagnosis	−0.009 (SE 0.004)	Product of a normal distribution with a mean of −8.3 and a SE of 3.83, and a normal distribution with a mean of 0.0011 and a SE of 0.0002	NICE guideline combination of social function and mapping to utility score[193]
Disutility associated with anaemia	0	Fixed	Assumed already captured in overall health-state utility values

TABLE 18 Model parameters and data sources (*continued*)

Parameter	Estimate	Distribution	Source
Transition probabilities			
Probability of developing osteoporosis with undiagnosed CD	OR vs. general population, 2.59 (95% CI 1.32 to 5.09) General population rates in *Table 16*	Log-normal on both OR and general population rate	• Godfrey *et al.*[236] • CPRD rate for general population
Probability of developing osteoporosis with diagnosed CD	OR vs. general population, 1.40 (95% CI 1.30 to 1.50) General population rates in *Table 16*	Log-normal on both OR and general population rate	• Ludvigsson *et al.*[235] • CPRD rate for general population
Probability of developing NHL with undiagnosed CD	Incidence ratio vs. general population, 4.7 (95% CI 2.9 to 7.3) General population rates in *Table 16*, and in tables s14–16 (see *Report Supplementary Material 1*)	Log-normal on both OR and general population rate	• Silano *et al.*[237] • CPRD rate for general population
Probability of developing NHL with diagnosed CD	Incidence ratio vs. general population, 3.28 (95% CI 1.49 to 6.28) General population rates in *Table 16*	Log-normal on both OR and general population rate	• Goldacre *et al.*[238] • CPRD rate for general population
Mortality probability from osteoporosis	Hazard ratio 3.5 (95% CI 3.28 to 3.74) times greater for male hip fracture patients than for controls and 2.4 (95% CI 2.31 to 2.50) times greater for female patients than for controls	Normal distributions on log-hazard ratios	Klop *et al.*[243]
Mortality probability from NHL	Log-hazard 2.092 (SD 0.006378)	Normal	Office for National Statistics 2018[241]

BNF, *British National Formulary*; FN, false negative; OR, odds ratio; TP, true positive.
a SE assumed to be one-tenth of the mean.

Analyses

Cost–benefit analysis to identify the optimal screening strategy

The objective of the model was to calculate the expected costs and health outcomes over a patient's lifetime for all screening strategies. Risk prediction strategies with sensitivity and specificity combinations of 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 were explored, followed by serological testing alone (IgA tTG alone, IgA tTG plus IgA EMA, and IgA EMA alone), combination of serological testing with genetic testing (HLA before or after the three serological testing strategies, with double-testing only for those with a 90% post-test probability after the first test) and no screening (routine diagnosis only) in adult men, adult women and children. Half-cycle corrections are applied to the Markov model; costs and QALYs were discounted at 3.5%, as recommended by NICE.[245] The analysis was fully probabilistic, with 1000 samples being generated for each population; no deterministic results are presented as the Markov model is non-linear.[246]

The total costs and QALYs were calculated for each of these strategies, along with the net benefit at £20,000 per QALY (i.e. total QALYs multiplied by £20,000 per QALY minus the total costs). Incremental costs, QALYs and net benefit were calculated relative to no screening. The probabilistic samples were

summarised by their means and Bayesian 95% CrIs. The probability of each decision being cost-effective, compared with no screening, at £20,000 per QALY was calculated by counting the proportion of samples for which the incremental net benefit was positive.

Further investigation was conducted in the testing combinations (e.g. IgA EMA plus HLA or IgA tTG) with the greatest net benefit and probability of being cost-effective for each population. If cost-effectiveness was similar to that of other tests, IgA tTG alone was selected because of its greater availability in UK laboratories.[247] These testing combinations were applied to the risk prediction strategies identified in *Table 5*. These were strategies with pre-test probabilities for blood test of 1%, 1.5%, 2%, 5%, 10% and 20%, with implied sensitivities (i.e. proportion of those with CD who have the diagnostic indicator combination) and specificities (i.e. proportion of those without CD who would have the diagnostic indicator combination) that can be run through the economic model. The cost-effectiveness of these strategies of interest were compared by total costs, QALYs and net benefits. The probability that each strategy has the greatest net benefit at various willingness-to-pay thresholds was also plotted, which is the cost-effectiveness acceptability curve (CEAC).

Value-of-information analysis to identify further research priorities

Decision uncertainty was quantified using a value-of-information analysis following the best-practice recommendations of the International Society for Pharmacoeconomics and Outcomes Research.[248–250] The total decision uncertainty was quantified using the expected value of perfect information (EVPI), whereas decision uncertainty related to a single parameter, or subset of parameters, was quantified using the expected value of partial perfect information (EVPPI). The ratio of the EVPPI for each parameter to the total EVPI was calculated to represent the relative importance of each parameter.[251] Generalised additive models were used to approximate the EVPPI for each parameter when calculating ratios with the EVPI.[252,253] As the exact values of the EVPPI may not be reliable, the EVPPI for parameters and parameter sets of interest were further estimated using multilevel Monte Carlo (MLMC) methods.[254]

The EVPI and the EVPPI are per person and must be scaled to the size of the population of interest. For CD, this is the total population of the UK, or 67,081,000 as of 2020.[255] It was assumed that 79% are aged ≥ 18 years and that 50% are female.[256] The prevalence of CD was taken as 1%.[2] This gives a total population of 263,465 for adult men or adult women, and 140,070 for children.

The EVPI and the EVPPI must also be summed, with discounting at 3.5%, over a 'technology horizon', which is the length of time for which the screening strategy recommendations are likely to remain relevant before newer testing techniques emerge. The technology horizon was conservatively set at 10 years. This gives a 10-year discounted total population of 2,267,824 for adult men or adult women, and of 1,205,679 for children.

The total population EVPI over 10 years was calculated. The total population EVPPI was also calculated for all utilities and disutilities, all rates of osteoporosis and NHL, all parameters related to a gluten-free diet (i.e. utility and effects of a gluten-free diet on NHL and osteoporosis rates), sensitivity and specificity of tests used in selected strategies of interest, and the probability of late diagnosis.

Software

The model was implemented in the R statistical programming language; the lower-level C/C± programming language was used for optimisation. This has well-documented advantages of efficiency, transparency and flexibility over the more commonly employed Microsoft Excel® (Microsoft Corporation).[257] The R package 'Bayesian cost-effectiveness analysis' (BCEA) was used to generate CEACs and estimate EVPPI via generalised additive models for individual parameters. The BCEA package was also used to plot the ratios of EVPPI to EVPI for each parameter using the info.rank() function.

Summary of modelling assumptions

A summary of modelling assumptions is provided in *Table 19*.

Results

In this section we present all the results of the cost-effectiveness analysis of case-finding strategies for adult men, adult women and children.

TABLE 19 Key assumptions of the cost-effectiveness model

Assumption	Justification
Biopsy is not associated with any major complications or death	No recent studies give evidence of major complications or death. One recent study of 13,233 patients undergoing outpatient OGD with biopsy over 5 years in the USA concluded that no patient was admitted because of complications.[213] A small disutility associated with the procedure and waiting time for diagnosis is assumed
Biopsy is perfectly accurate	In reality, a biopsy will not always provide perfect results; however, it is the current gold standard and people are treated on the basis of their biopsy results. The 2015 NICE health economic analysis[193] of screening strategies also made this assumption
It is assumed that the percentage of patients being diagnosed with CD after screening (i.e. initially missed) requiring a confirmatory biopsy before diagnosis is 70%	Based on clinical advice that 30%, with a plausible range, of patients diagnosed with CD do not require a confirmatory biopsy. This is in accordance with recent research indicating high diagnostic accuracy of tests alone[70,89,220,221]
The only additional cost incurred by people with a false-positive diagnosis of CD is the cost of a gluten-free diet for a short period of time No further costs are incurred by people with a true-negative diagnosis	Patients without CD who are screened for CD are assumed not to have costs or health outcomes that are different from those of other non-CD patients who were not screened for CD. As such, we model only the long-term consequences of patients who have CD (whether diagnosed or undiagnosed)
NHL is associated with a one-off lifetime cost of £18,396 (95% CI £18,377 to £18,415) with a log-normal distribution	Treatment for NHL is usually complete within 5 years, with most costs estimated to fall within 5 years. The model was used to estimate the cost factors of different survival times when estimating the treatment costs, so patients would incur fewer costs if they died within a shorter time
Annual cost/disutility of osteoporosis is equal to annual probability of hip, vertebral and wrist fractures multiplied by cost/disutility of each type of fracture	This is the approach taken in the NICE model.[193] The cost and disutility of osteoporosis mainly relates to the risk of fracture, of which hip, vertebral and wrist are common types
Treatment for IDA among CD patients is by over-the-counter iron tablets only.	This was based on clinical opinion
IDA disutility is already captured in utility values for undiagnosed CD/diagnosed CD sourced from Violato and Gray[231]	Violato and Gray[231] reported that 64.8% of their population had anaemia prior to diagnosis and 14.5% had anaemia after
Mortality in model is equal to general population mortality, with excess mortality assigned to patients who develop NHL or osteoporosis	
To get to a diagnosis of CD, a person's first appointment is with either a nurse or a GP, with a 50% chance of this being with one or the other. This is followed by an appointment with a phlebotomist/nurse and then by another GP appointment. Following that, a patient has, on average, one gastroenterologist and two dietitian appointments before diagnosis	This was the most common route to diagnosis, as agreed by clinicians and patients on the research team

Adult men

We first compared a range of combinations of sensitivities and specificities for a hypothetical diagnostic indicator (or indicator combinations) in population of the adult men. *Figure 14* plots the incremental net benefit at £20,000 per QALY of each sensitivity/specificity combination of an indicator combined with each serological testing strategy, compared with no screening, among adult men. The central estimates are the mean incremental net benefit, with the upper and lower CrIs represented by the upper and lower lines.

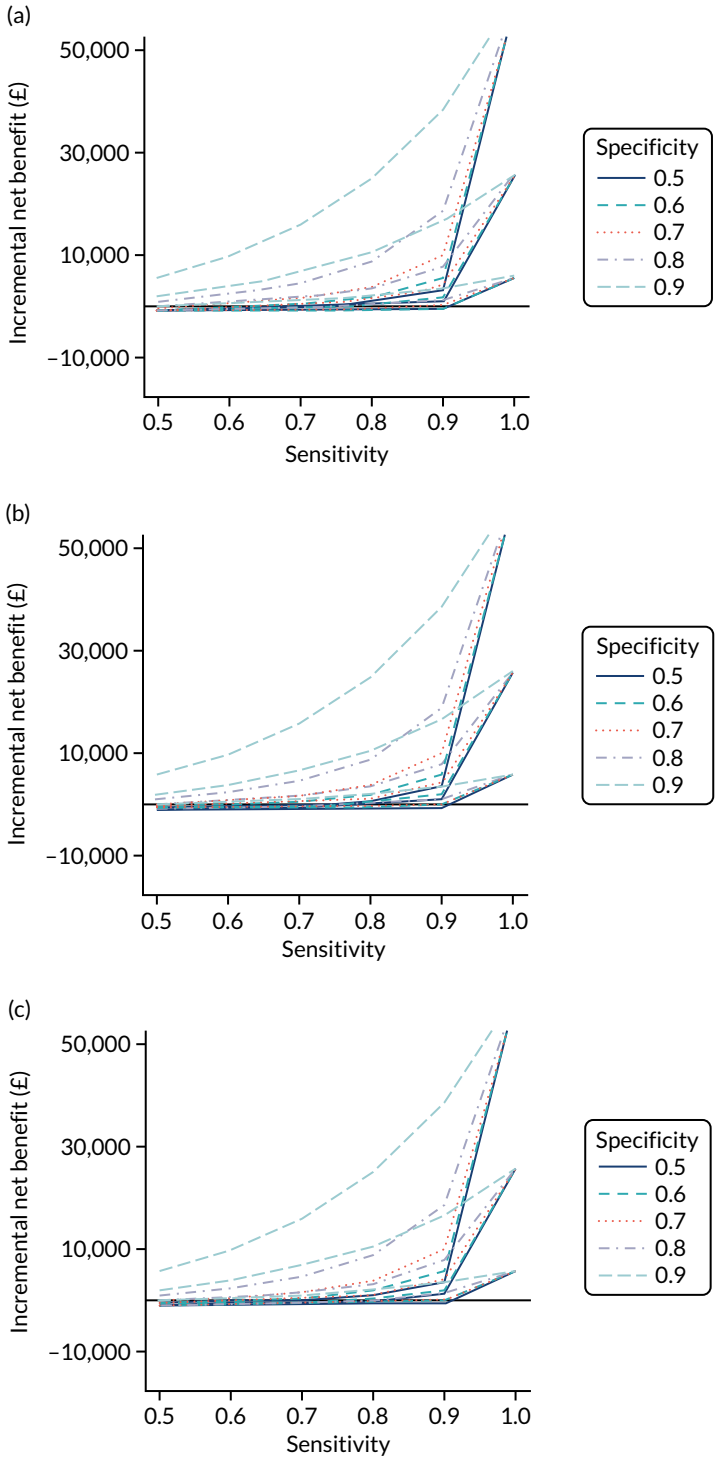

FIGURE 14 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI. (*continued*)

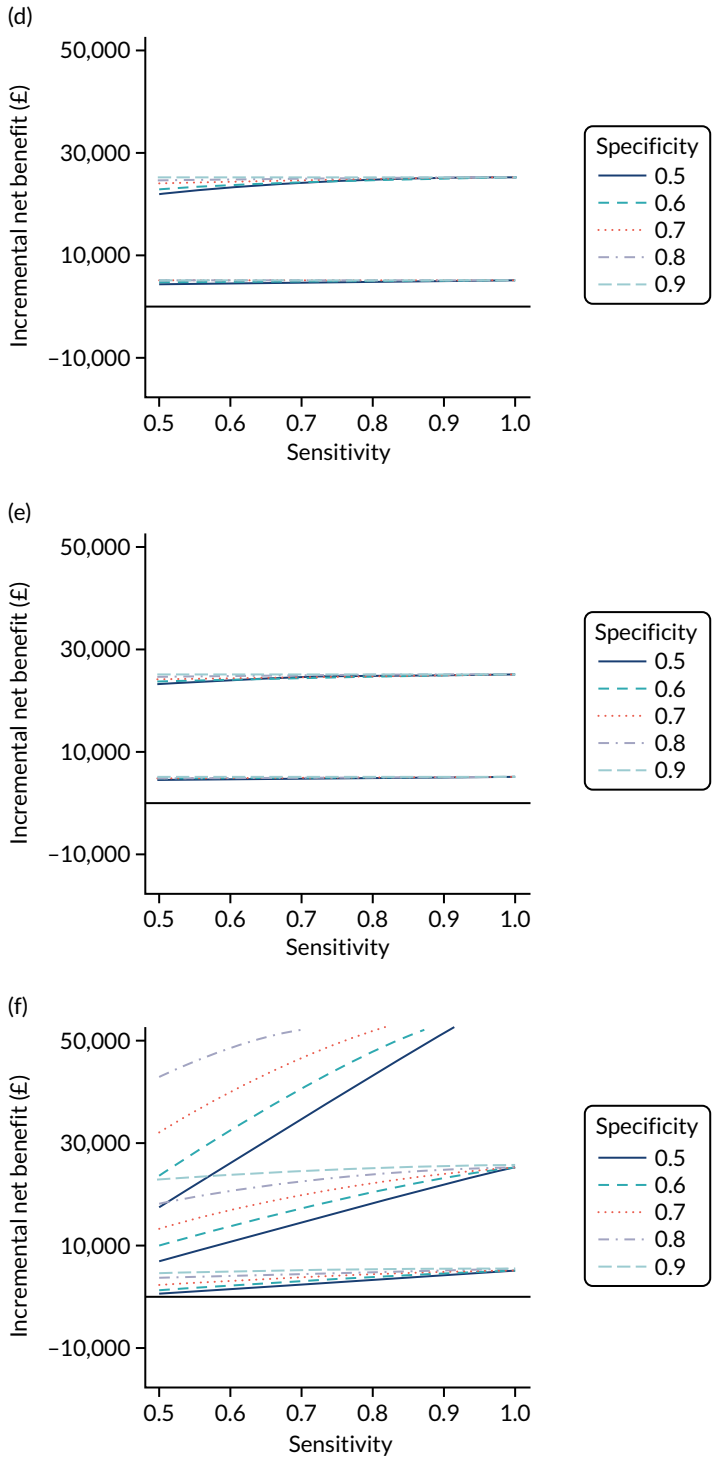

FIGURE 14 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI. (*continued*)

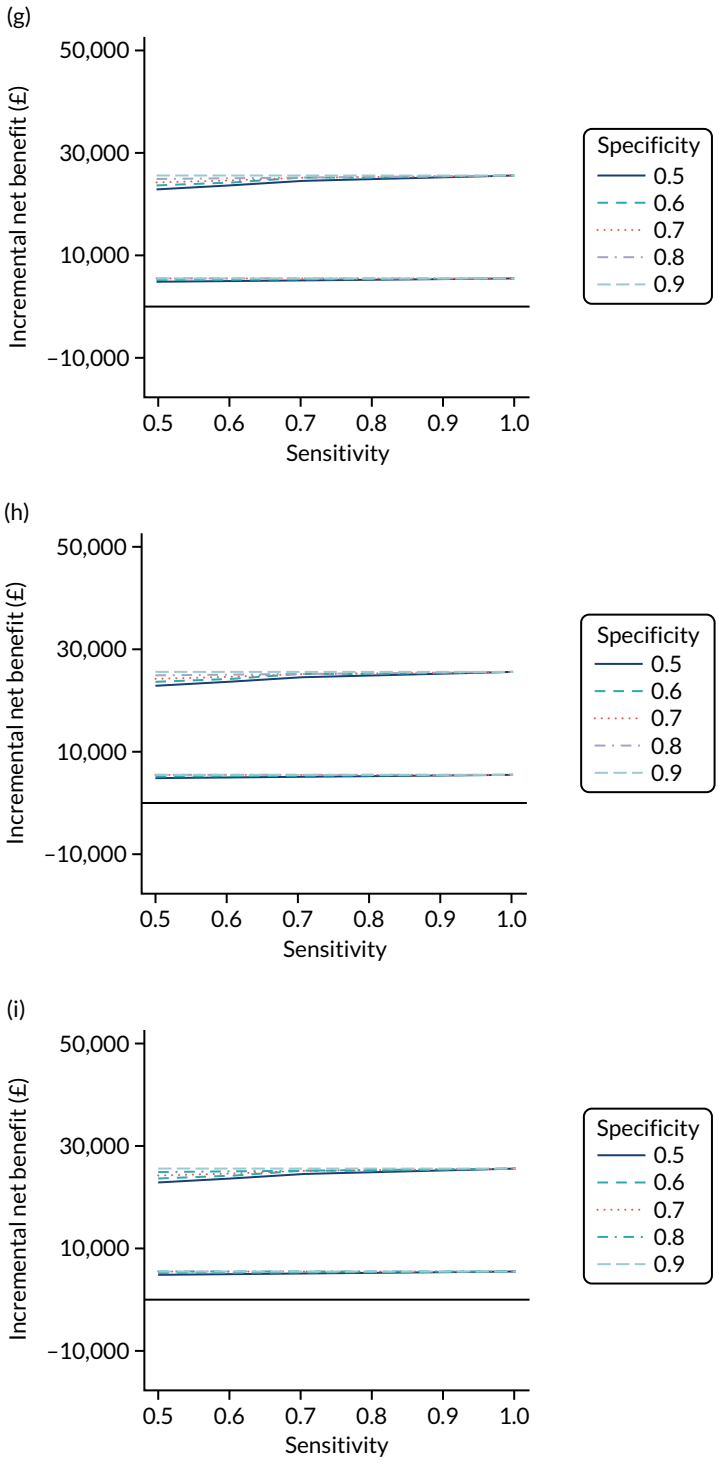

FIGURE 14 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI.

Figure 14 shows that, for strategies using only serological tests (i.e. without HLA), incremental net benefit is positive only when diagnostic indicator sensitivity is > 0.9 or both the specificity and sensitivity are > 0.8. For the serological tests including HLA, the incremental net benefit is positive regardless of the accuracy of the diagnostic indicator, although the lower limit of the 95% CrI shows that there is some uncertainty. The combinations using only the IgA EMA serological test plus HLA (i.e. IgA EMA plus HLA or HLA plus IgA EMA) are more cost-effective than strategies using IgA tTG

plus HLA and comparable in cost-effectiveness to tests using all three of IgA EMA, IgA tTG and HLA. HLA being administered before or (as confirmation if post-test probability < 90%) after IgA EMA or IgA tTG plus EMA does not affect cost-effectiveness, but it is most cost-effective if used before IgA tTG.

Figure 15 plots the probability that each combination of diagnostic indicator sensitivity and specificity is cost-effective for each test combination at £20,000 per QALY (i.e. proportion of simulations having a positive incremental net benefit at £20,000 per QALY, compared with no screening). It again shows that the only strategies using serological tests alone that have a probability of > 50% of being cost-effective are those diagnostic indicators with a sensitivity of > 0.9 or both specificity and sensitivity of > 0.8. As expected, the combinations of tests with the highest probability of being cost-effective are those with a specificity of 0.9 and a sensitivity of 0.9 or 1. The serological tests including HLA have a high probability of being cost-effective regardless of the combination of sensitivity and specificity of the diagnostic indicator. Strategies using IgA EMA or IgA tTG alone with HLA have a probability of cost-effectiveness that is similar to that of combinations using all three of IgA EMA, HLA and IgA tTG.

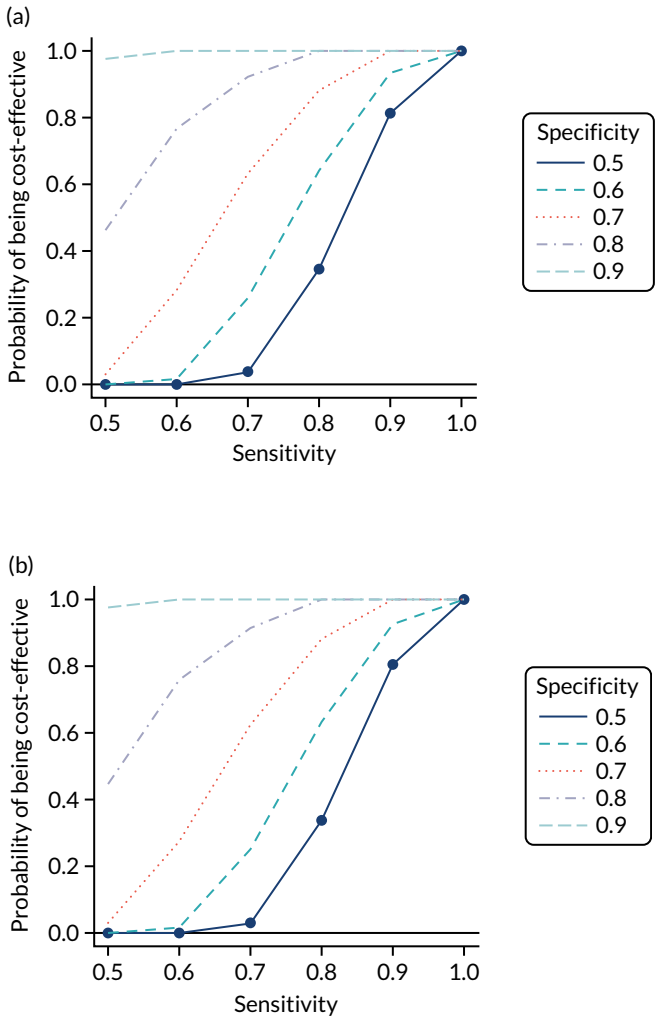

FIGURE 15 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

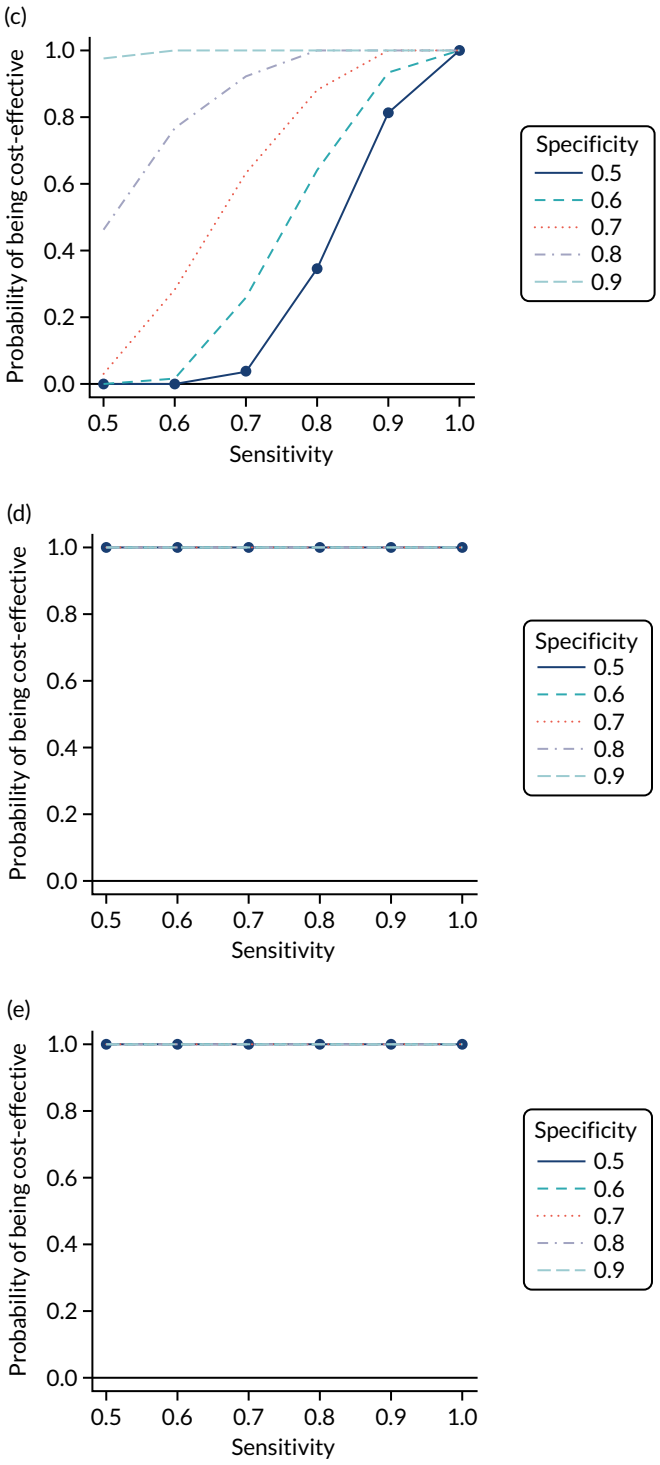

FIGURE 15 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

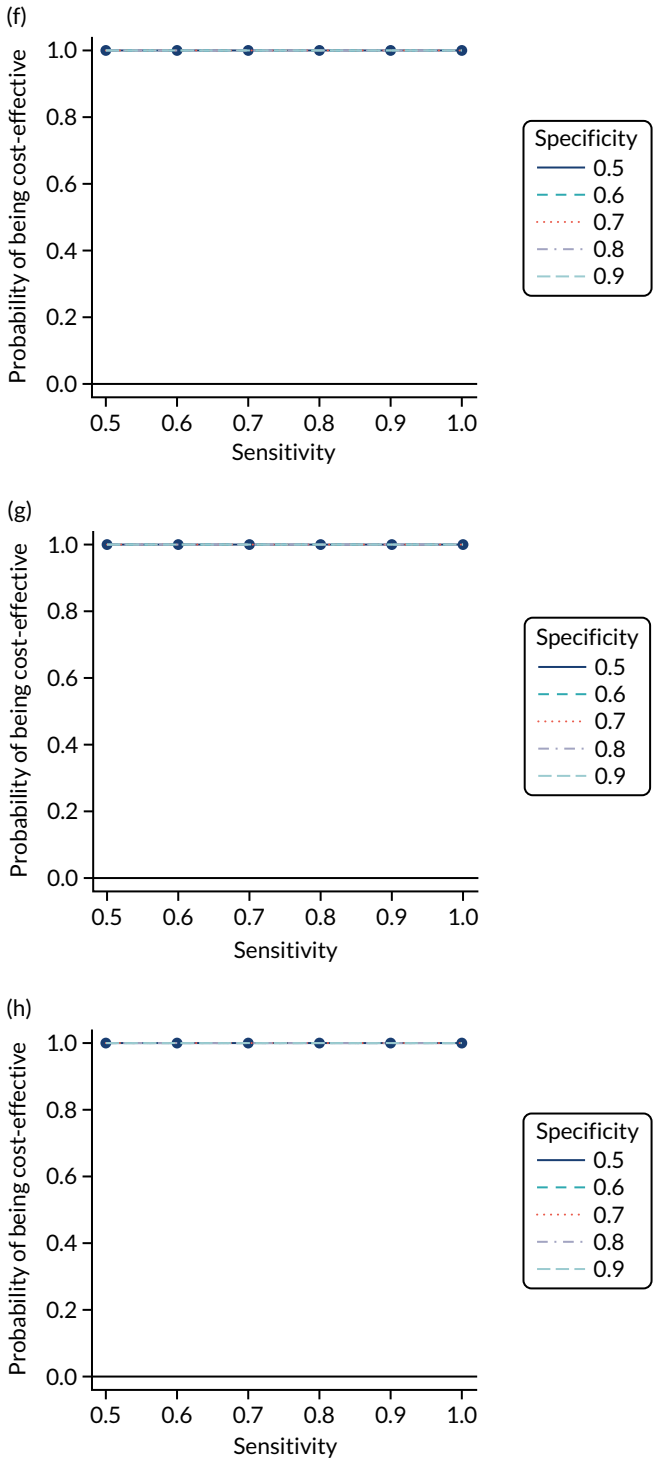

FIGURE 15 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

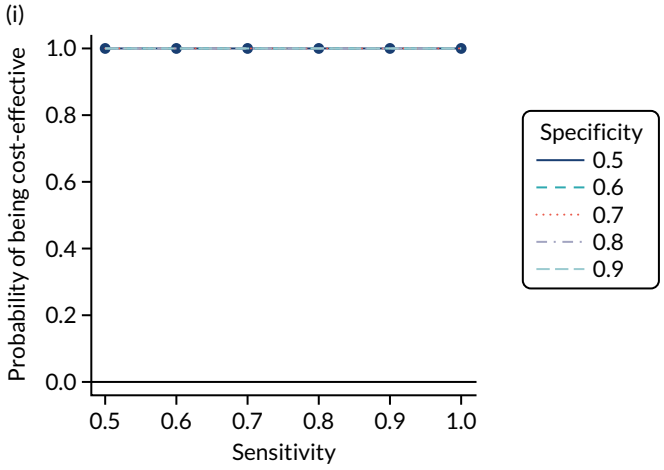

FIGURE 15 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) among adult men. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG.

In general, strategies employing IgA tTG and IgA EMA have similar incremental net benefits and probabilities of being cost-effective; given the greater availability of IgA tTG in the UK, we chose this as one of our strategies of interest.[247] Although all strategies employing HLA have higher incremental net benefit and probability of cost-effectiveness, IgA tTG plus HLA performs worst. There is also limited benefit to adding IgA tTG to strategies using IgA EMA and HLA, and limited difference between using IgA EMA or HLA first, so we used IgA EMA followed by HLA for our second testing combination of interest. Again, owing to its wide availability and its having high incremental net benefit and probability of cost-effectiveness, we chose HLA plus IgA tTG as a final test of interest. These selections were combined with the risk prediction strategies of *Table 5*.

Table 20 shows the estimated costs, QALYs and incremental net benefit, compared with no screening, for each of these strategies of interest. All combinations have positive incremental net benefit compared with no screening. If using only the serological test IgA tTG, with a pre-test probability of 1%, it is the most cost-effective strategy (greatest incremental net benefit at £20,000 per QALY), with the highest costs but also the largest number of QALYs. The net benefits of the IgA EMA plus HLA and the HLA plus IgA tTG strategies are very similar to each other and to those of IgA tTG with a pre-test probability of 1%, and the 95% CrIs are completely overlapping. This indicates that there is little or no difference between these strategies in cost-effectiveness.

Figure 16 plots the CEACs, which show the probability that each testing strategy is optimal (i.e. has the highest net benefit) at each willingness-to-pay threshold for an additional QALY. None of the probabilities is > 60%, suggesting limited certainty that any of the strategies is most cost-effective. At £10,000–30,000 per QALY, the strategy with greatest probability of being cost-effective is HLA plus IgA tTG at a pre-test probability of 5% (i.e. 5% HLA plus IgA tTG); above this range, 1% IgA EMA plus HLA has the greatest probability of being cost-effective. However, the CEAC does not account for the magnitude of differences between net benefits, which, as reported in *Table 20*, are negligible with overlapping 95% CrIs.

Table S19 (see *Report Supplementary Material 1*) provides the proportion of time spent in each state for adult men on the strategies of interest. Compared with other pre-test probability strategies with the same serological tests, the 1% IgA EMA strategy has the greatest proportion of time in the CD, gluten-free diet, no-complications state and the least time in the undiagnosed states. Osteoporosis appears to be the complication most patients spend time in, with NHL being up to six times less common. The HLA strategies have a greater proportion of time in the CD, gluten-free diet, no-complications state and less time in the

TABLE 20 Costs, QALYs and incremental net benefits, at £20,000 per QALY, associated with strategies of interest for adult men

Pre-test probability for blood test (%)	Sensitivity of indicator	Specificity of indicator	Strategy	Mean (95% CrI)		
				Costs (£)	QALYs	Incremental net benefit at £20,000 per QALY vs. no screening (£)
No screening				17,389 (14,011 to 19,332)	18.31 (16.39 to 19.54)	0 (0 to 0)
1	1	0	IgA tTG	20,468 (20,152 to 20,778)	19.68 (19.14 to 20.04)	24,331 (5080 to 56,493)
1.5	0.87	0.431	IgA tTG	18,325 (15,069 to 20,186)	18.36 (16.52 to 19.56)	161 (–676 to 1530)
2	0.79	0.61	IgA tTG	18,236 (14,990 to 20,091)	18.37 (16.53 to 19.56)	355 (–549 to 1838)
5	0.579	0.889	IgA tTG	18,270 (15,286 to 19,963)	18.49 (16.83 to 19.6)	2838 (187 to 7218)
10	0.322	0.971	IgA tTG	18,567 (16,137 to 19,955)	18.72 (17.37 to 19.66)	7179 (1292 to 16,949)
20	0.107	0.996	IgA tTG	19,267 (18,020 to 20,053)	19.21 (18.43 to 19.82)	16,114 (3482 to 37,161)
1	1	0	IgA EMA plus HLA	20,841 (20,546 to 21,147)	19.73 (19.19 to 20.1)	25,060 (5050 to 58,568)
1.5	0.87	0.431	IgA EMA plus HLA	20,535 (20,229 to 20,844)	19.71 (19.17 to 20.08)	24,884 (5204 to 57,564)
2	0.79	0.61	IgA EMA plus HLA	20,430 (20,123 to 20,737)	19.71 (19.17 to 20.08)	24,981 (5300 to 57,672)
5	0.579	0.889	IgA EMA plus HLA	20,330 (20,034 to 20,641)	19.72 (19.18 to 20.09)	25,262 (5415 to 58,394)
10	0.322	0.971	IgA EMA plus HLA	20,350 (20,053 to 20,655)	19.72 (19.18 to 20.09)	25,237 (5331 to 58,488)
20	0.107	0.996	IgA EMA plus HLA	20,412 (20,123 to 20,716)	19.71 (19.18 to 20.09)	25,135 (5186 to 58,444)
1	1	0	HLA plus IgA tTG	20,837 (20,545 to 21,148)	19.73 (19.19 to 20.1)	25,059 (5055 to 58,561)
1.5	0.87	0.431	HLA plus IgA tTG	20,541 (20,235 to 20,850)	19.71 (19.18 to 20.08)	24,957 (5217 to 57,825)
2	0.79	0.61	HLA plus IgA tTG	20,437 (20,131 to 20,747)	19.71 (19.18 to 20.08)	25,048 (5311 to 57,918)
5	0.579	0.889	HLA plus IgA tTG	20,338 (20,035 to 20,645)	19.72 (19.18 to 20.09)	25,273 (5409 to 58,467)
10	0.322	0.971	HLA plus IgA tTG	20,358 (20,056 to 20,665)	19.72 (19.18 to 20.09)	25,231 (5316 to 58,506)
20	0.107	0.996	HLA plus IgA tTG	20,417 (20,124 to 20,726)	19.71 (19.18 to 20.09)	25,126 (5176 to 58,438)

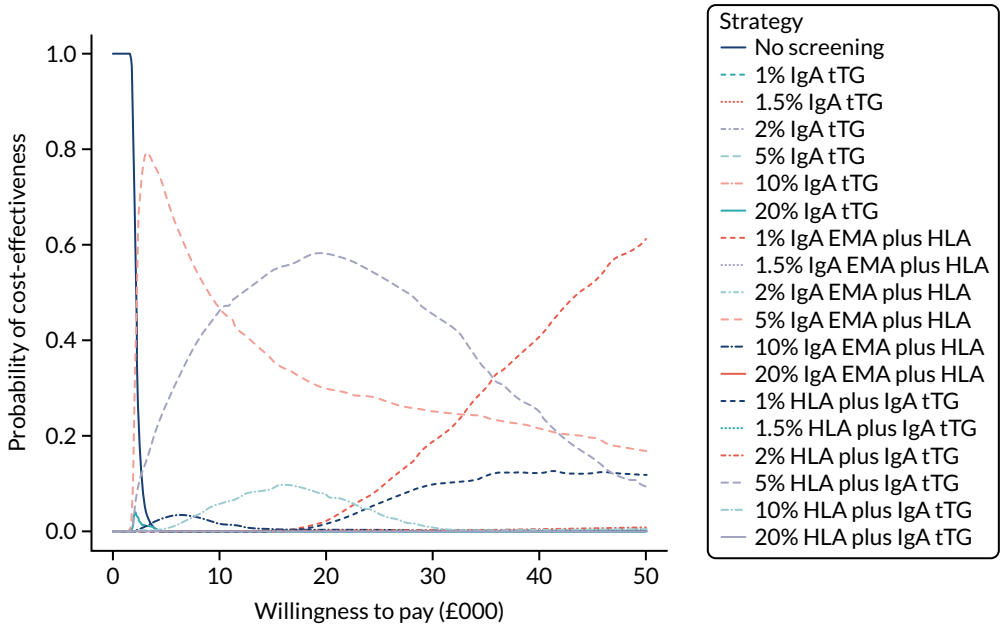

FIGURE 16 Cost-effectiveness acceptability curves for strategies of interest for adult men.

undiagnosed states than any IgA EMA strategies. These strategies all have very similar proportions of time across the different pre-test probabilities, with only minor differences between the CD, gluten-free diet state and the undiagnosed CD, no-complications state. Overall, cost-effectiveness appears to be mostly driven by time spent in the CD, gluten-free diet, no-complications state; the CD, gluten-free diet, osteoporosis state; and the undiagnosed CD, osteoporosis state.

The ratio of EVPPI to EVPI for each parameter is illustrated in *Figure 17*. The probability of late diagnosis and the sensitivity of HLA testing are the most influential parameters. The impact of gluten-free diet on the probability of developing osteoporosis and the accuracy of IgA EMA testing have low influence, and all other parameters appear to have no influence, on the results.

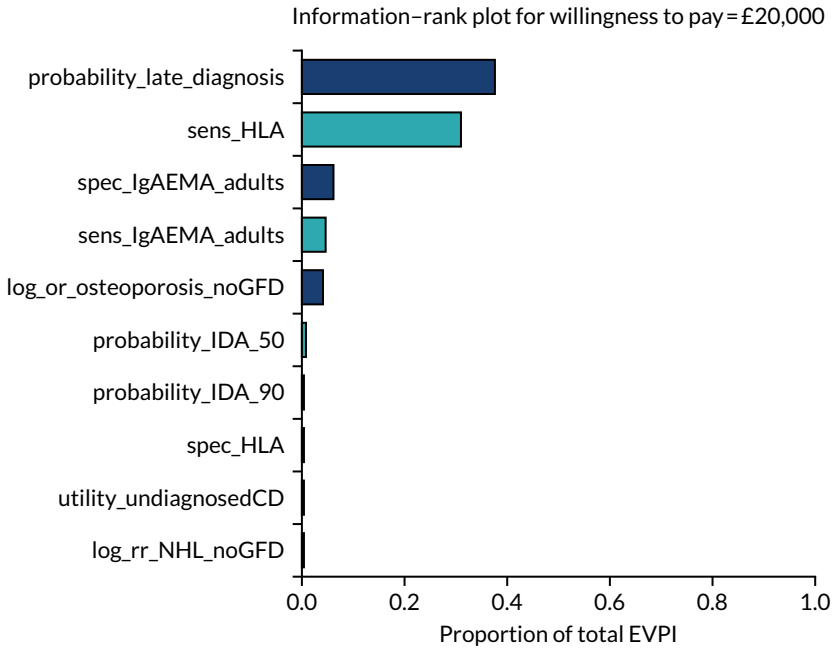

FIGURE 17 Ratio of EVPPI for each parameter to total EVPI among adult men. Only the 10 most influential parameters are included; the remaining parameters have minimal influence on the results. GFD, gluten-free diet; log_or_osteoporosis_noGFD, log-odds ratio of developing osteoporosis, not on a GFD, compared with being on a GFD; log_rr_NHL_noGFD, log-risk ratio of developing NHL, not on a GFD, compared with being on a GFD, for coeliac patients; probability_IDA_50, prevalence of IDA at age 50 years; probability_IDA_90, prevalence of IDA at age 90 years; sens, sensitivity; spec, specificity.

The total EVPI and EVPPI for parameter sets of interest are summarised in *Table 21*. The total population EVPI for men is £25.7M, indicating potential value in conducting further research. The EVPPI for parameter sets indicates that the greatest potential value lies in a study of probabilities of late diagnosis or on test-accuracy parameters. This aligns with the ranking in *Figure 17*.

Adult women

Figure 18 plots the incremental net benefit of each sensitivity/specificity combination of a diagnostic indicator (or combination of indicators) combined with each serological test, compared with no screening, for adult women. The central estimates are the mean incremental net benefit, with the upper and lower CrIs represented by the upper and lower lines.

The results are extremely similar to those for adult men. *Figure 18* shows that, for the serological tests without HLA, the incremental net benefit at £20,000 per QALY is positive only when the diagnostic indicator sensitivity is > 0.9 or both the specificity and sensitivity are > 0.8. For the serological tests including HLA, the incremental net benefit is positive regardless of the accuracy of the diagnostic indicator. The combinations using only the IgA EMA serological test plus HLA are more cost-effective than strategies using IgA tTG plus HLA and are comparable in cost-effectiveness to tests using all of EMA, tTG and HLA. Using HLA before or after EMA or tTG plus EMA does not affect cost-effectiveness, but it appears to be most cost-effective if used before IgA tTG alone.

Figure 19 plots the probability that each combination of diagnostic indicator sensitivity and specificity is cost-effective for each test combination. Results are again nearly identical to those for adult men. The serological tests including HLA have a high probability of being cost-effective regardless of the combination of sensitivity and specificity of the risk test. Strategies using IgA EMA or IgA tTG alone and HLA have a similar probability of cost-effectiveness to combinations using all three of IgA EMA, HLA and IgA tTG.

TABLE 21 Total EVPI and EVPPI for parameter sets of interest

Parameter set	Men		Women		Children[a]	
Total population size (*n*)	263,465		263,465		140,070	
Discounted population size (*n*)	2,267,824		2,267,824		1,205,679	
	Per person (£)	***Population (£)***	***Per person (£)***	***Population (£)***	***Per person (£)***	***Population (£)***
Total EVPI	11.32	25,679,685	34.85	79,040,182	15.28	18,420,293
Utilities and disutilities	3.72	8,425,612	1.62	3,663,585	0.93	1,117,066
Rates of osteoporosis and NHL	2.84	6,449,814	10.08	22,849,058	0.40	486,521
GFD effect	3.02	6,850,323	10.89	24,702,170	0.26	316,551
Test accuracies	6.81	15,447,753	18.98	43,035,778	6.48	7,812,603
Probability of late diagnosis	8.01	18,159,091	30.22	68,534,495	8.76	10,561,800

GFD, gluten-free diet; NR, not reported.

a MLMC method estimates for children failed to converge. Gaussian process estimates are presented, but were run only on the utilities estimate and in this set were also unstable.

Notes

Values for adult men and women were estimated using the MLMC method; Gaussian process estimates are presented for children. All EVPI and EVPPI values are in Great British pounds. Higher values indicate greater impact on results and greater value in conducting further research.

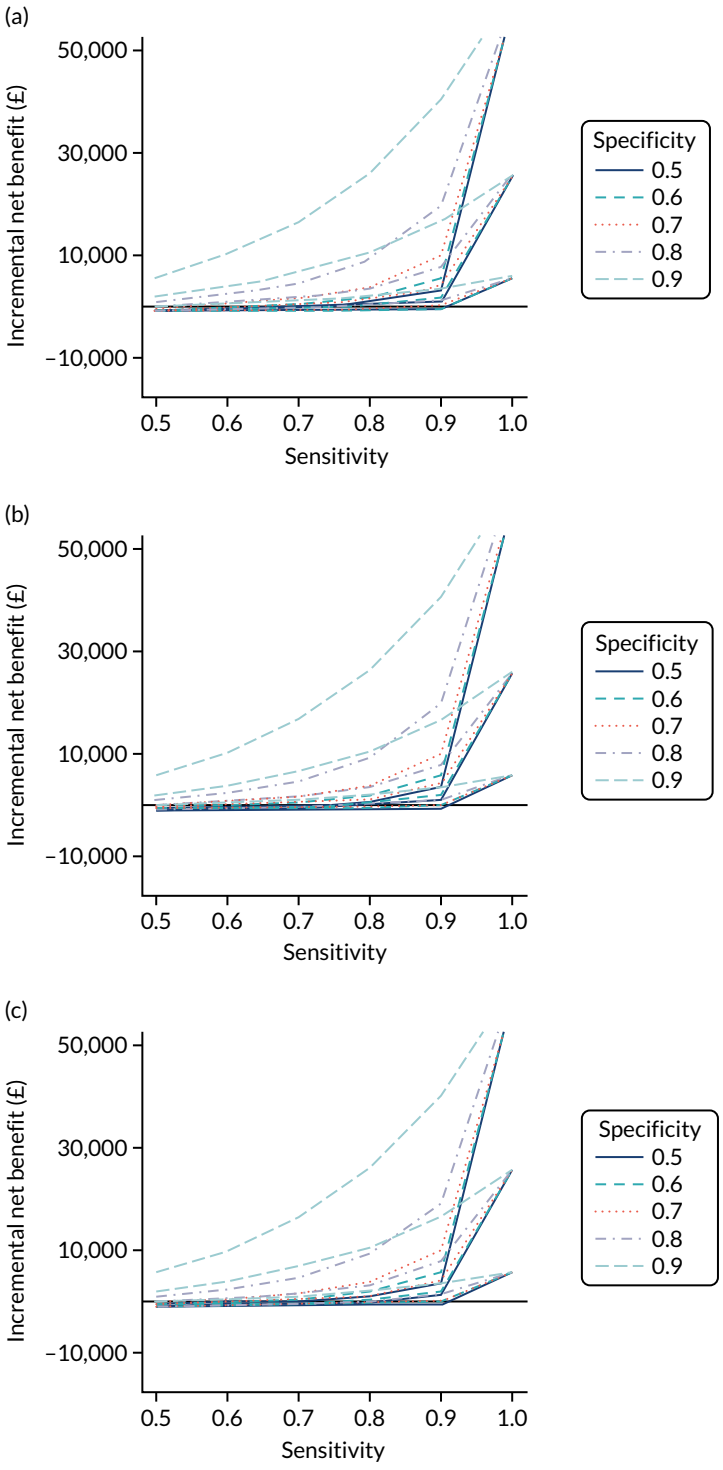

FIGURE 18 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (x-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines represent the 95% CrI. (*continued*)

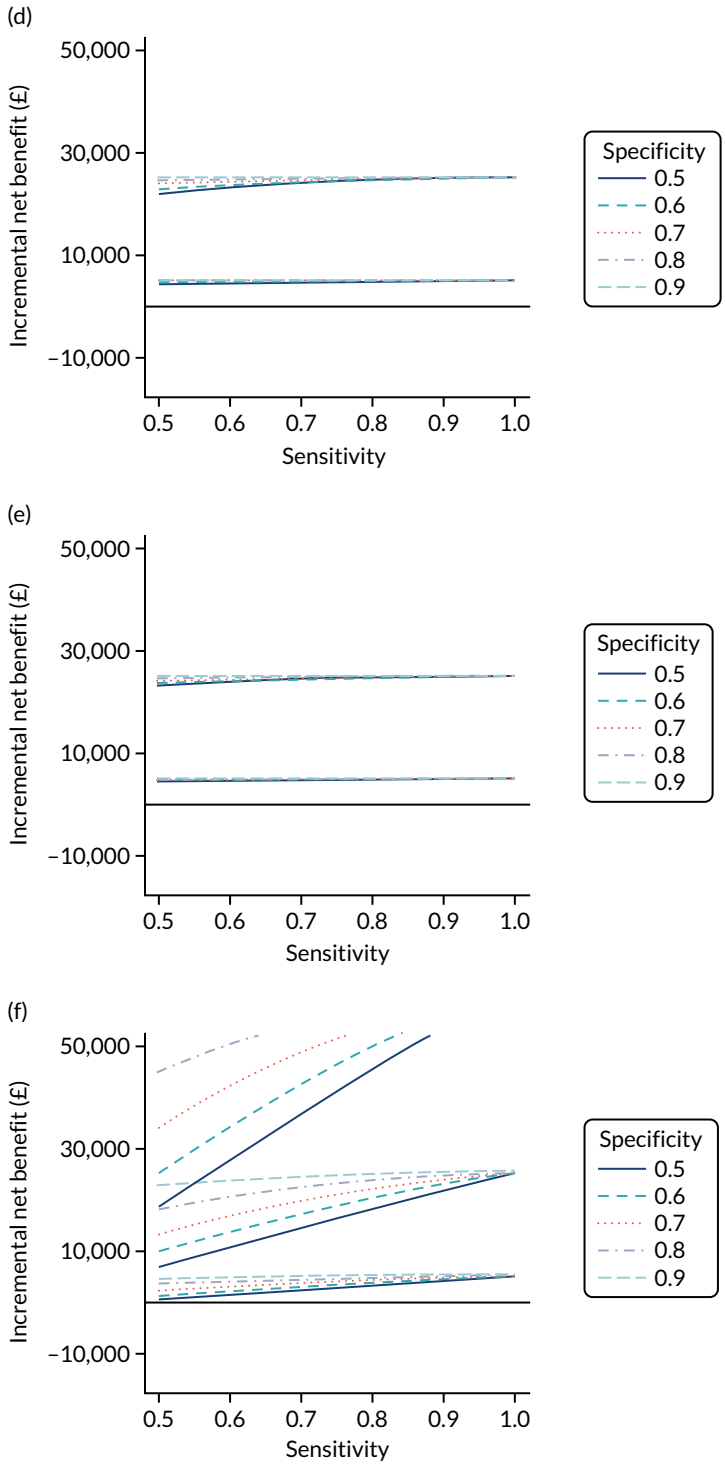

FIGURE 18 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines represent the 95% CrI. (*continued*)

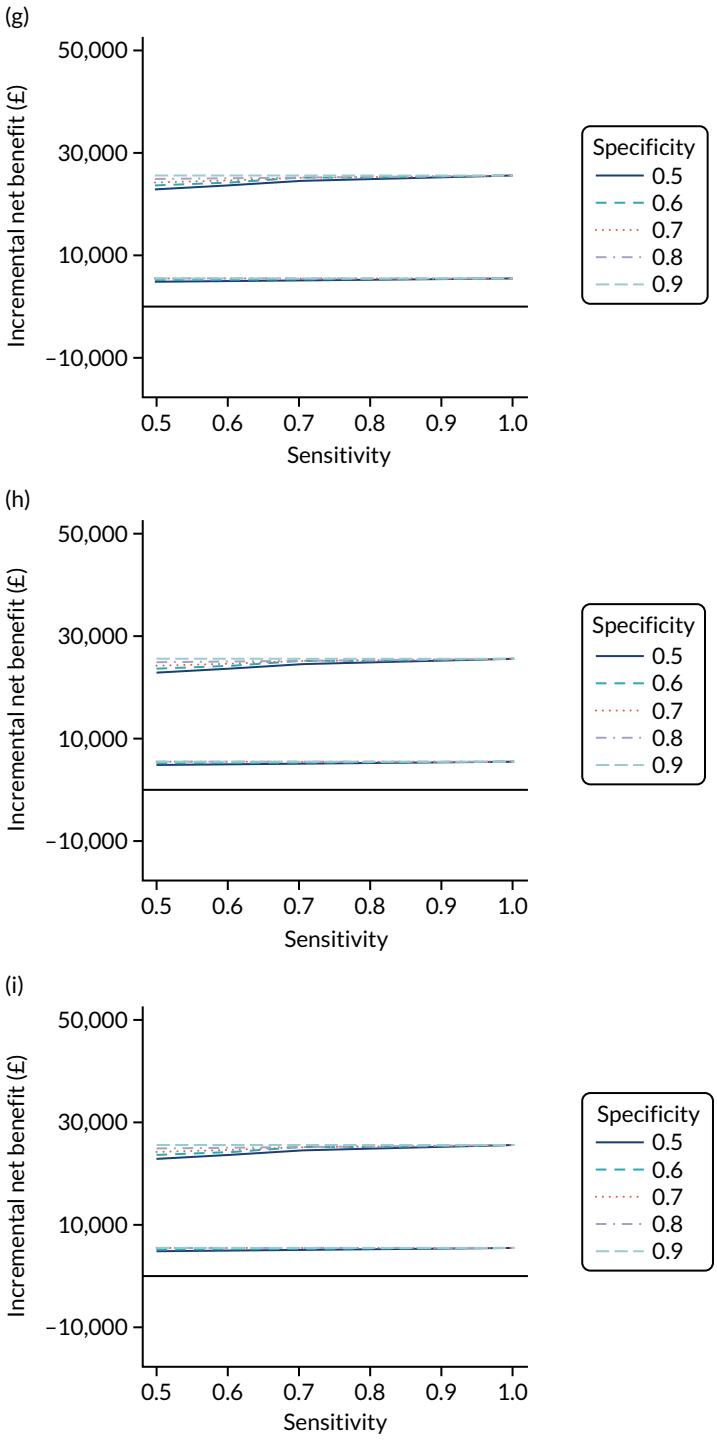

FIGURE 18 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (x-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines represent the 95% CrI.

As for adult men, we select the testing strategies IgA tTG alone, IgA EMA plus HLA, and HLA plus IgA tTG to combine with the various risk prediction strategies of *Table 5*. This is again justified as strategies using IgA tTG and IgA EMA have similar incremental net benefits and probabilities of being cost-effective, IgA tTG plus HLA performs worst among strategies with HLA, there is limited difference between IgA tTG plus EMA plus HLA and IgA EMA plus HLA (i.e. not employing tTG), and HLA plus the widely available IgA tTG has similar cost-effectiveness to other strategies. There is also limited difference between strategies applying HLA before or after serological tests.

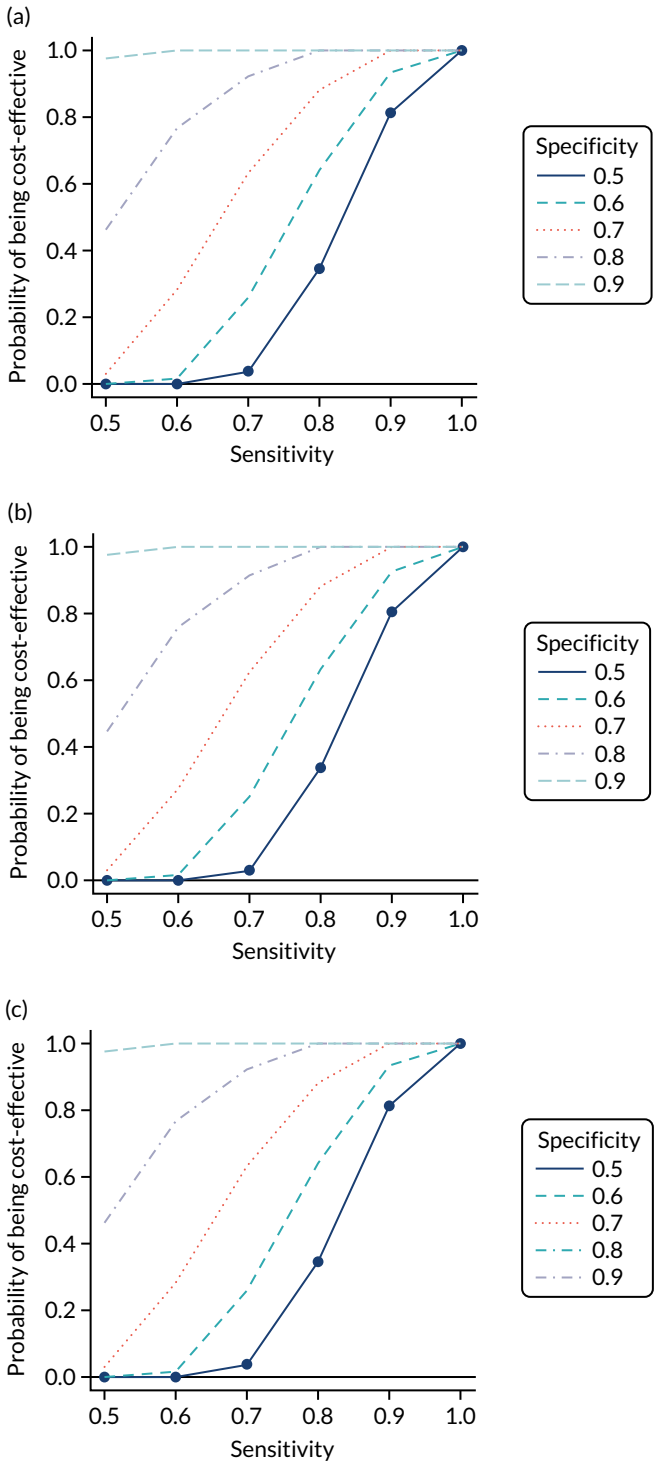

FIGURE 19 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (x-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

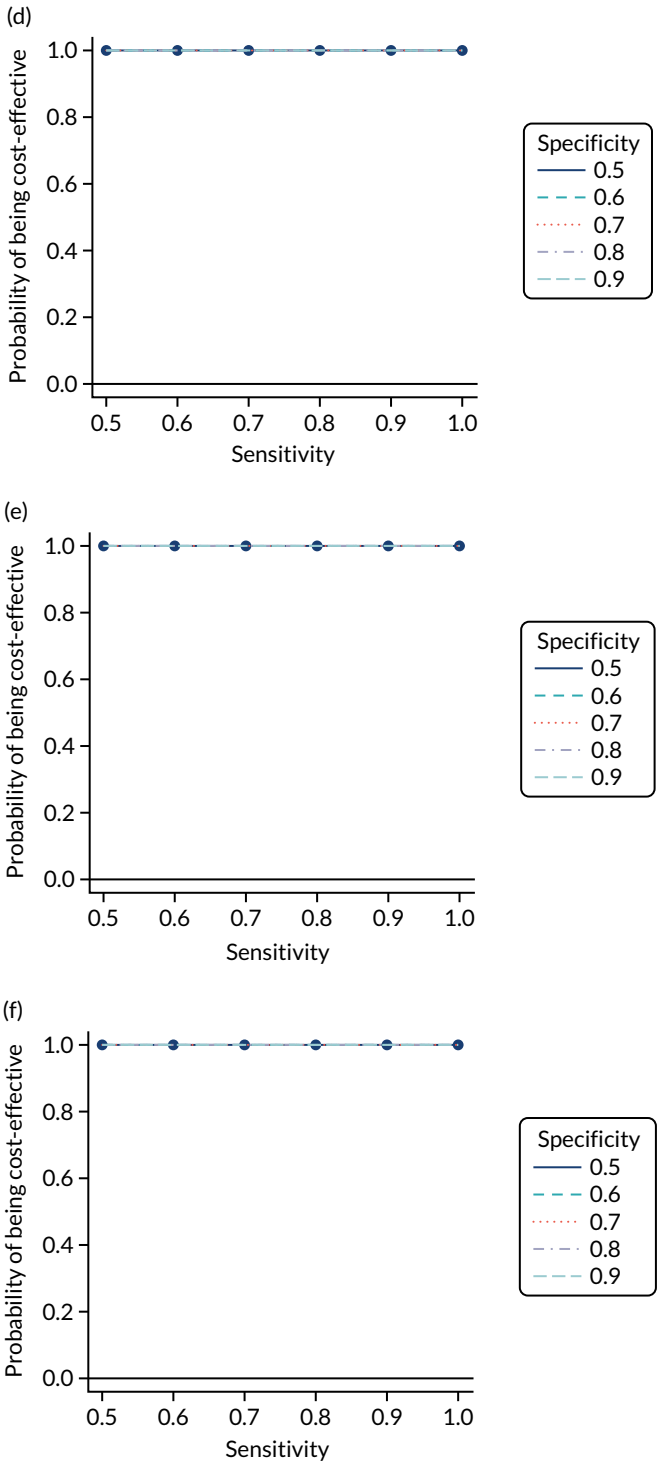

FIGURE 19 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

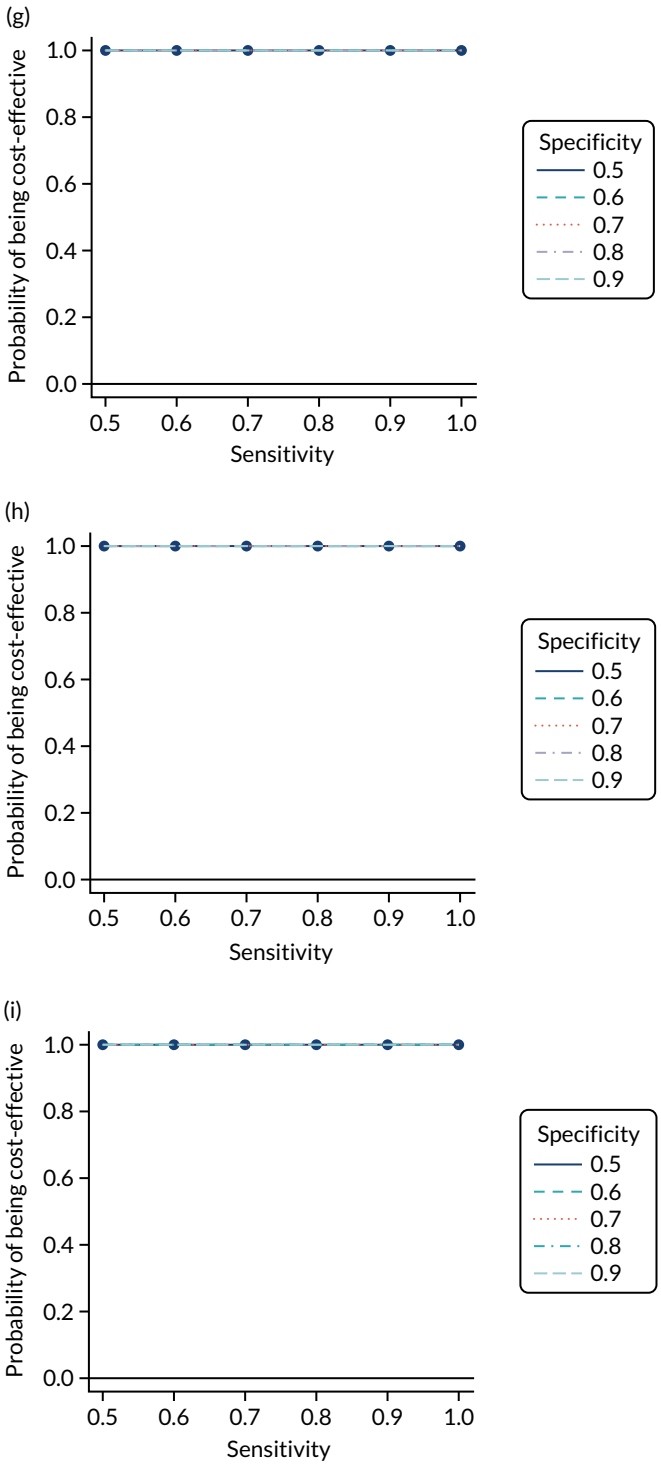

FIGURE 19 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for adult women. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG.

Table 22 shows the estimated costs, QALYs and incremental net benefit, compared with no screening, for each of these strategies of interest. All combinations, apart from pre-test probabilities of 1.5% with IgA tTG, have positive incremental net benefits, compared with no screening. If using only IgA tTG, a pre-test probability of 1% is the most cost-effective strategy (greatest incremental net benefit at £20,000 per QALY), with the highest costs but also the largest number of QALYs. As with men, the net

TABLE 22 Costs, QALYs and incremental net benefits, at £20,000 per QALY, associated with strategies of interest for adult women

Pre-test probability for blood test (%)	Sensitivity	Specificity	Strategy	Mean (95% CrI)		
				Costs (£)	QALYs	Incremental net benefit at £20,000 per QALY vs. no screening (£)
No screening				17,673 (14,159 to 19,645)	18.68 (16.72 to 19.9)	0 (0 to 0)
1	1	0	IgA tTG	20,771 (20,469 to 21,082)	20.05 (19.59 to 20.42)	24,382 (4829 to 59,154)
1.50	0.841	0.448	IgA tTG	18,585 (15,184 to 20,501)	18.72 (16.84 to 19.91)	−27 (−716 to 1197)
2	0.758	0.628	IgA tTG	18,500 (15,118 to 20,407)	18.73 (16.86 to 19.91)	228 (−575 to 1660)
5	0.387	0.926	IgA tTG	18,458 (15,268 to 20,262)	18.81 (17.05 to 19.93)	1880 (−63 to 5360)
10	0.107	0.99	IgA tTG	18,706 (15,970 to 20,247)	19 (17.48 to 19.98)	5428 (807 to 13,728)
20	0.002	1	IgA tTG	19,214 (17,329 to 20,319)	19.35 (18.28 to 20.1)	11,835 (2322 to 28,874)
1	1	0	IgA EMA plus HLA	21,143 (20,863 to 21,447)	20.11 (19.62 to 20.46)	25,115 (4766 to 61,286)
1.50	0.841	0.448	IgA EMA plus HLA	20,817 (20,522 to 21,131)	20.08 (19.6 to 20.44)	24,844 (4934 to 60,463)
2	0.758	0.628	IgA EMA plus HLA	20,714 (20,419 to 21,030)	20.08 (19.6 to 20.44)	24,981 (5033 to 60,663)
5	0.387	0.926	IgA EMA plus HLA	20,598 (20,319 to 20,904)	20.09 (19.61 to 20.44)	25,244 (5118 to 61,069)
10	0.107	0.99	IgA EMA plus HLA	20,629 (20,358 to 20,927)	20.09 (19.61 to 20.45)	25,259 (5033 to 61,175)
20	0.002	1	IgA EMA plus HLA	20,683 (20,407 to 20,993)	20.09 (19.61 to 20.44)	25,210 (4927 to 61,189)
1	1	0	HLA plus IgA tTG	21,139 (20,856 to 21,442)	20.11 (19.62 to 20.46)	25,114 (4770 to 61,277)
1.50	0.841	0.448	HLA plus IgA tTG	20,824 (20,533 to 21,138)	20.08 (19.61 to 20.44)	24,935 (4951 to 60,666)
2	0.758	0.628	HLA plus IgA tTG	20,722 (20,434 to 21,030)	20.08 (19.61 to 20.44)	25,058 (5043 to 60,805)
5	0.387	0.926	HLA plus IgA tTG	20,607 (20,333 to 20,915)	20.09 (19.61 to 20.45)	25,268 (5110 to 61,127)
10	0.107	0.99	HLA plus IgA tTG	20,638 (20,366 to 20,938)	20.09 (19.61 to 20.45)	25,259 (5018 to 61,192)
20	0.002	1	HLA plus IgA tTG	20,690 (20,415 to 20,998)	20.09 (19.61 to 20.44)	25,203 (4914 to 61,189)

benefits of all IgA EMA plus HLA and HLA plus IgA tTG strategies are very similar to each other and to those of IgA tTG with a pre-test probability of 1%, and the 95% CrIs are completely overlapping. This again indicates little difference between the cost-effectiveness of these strategies.

Figure 20 plots the CEACs, which show the probability that each testing strategy is optimal (i.e. has the highest net benefit) at each willingness-to-pay threshold for an additional QALY. None of the probabilities exceeds 50%, indicating little certainty that the 1% IgA tTG, the IgA EMA plus HLA or the HLA plus IgA tTG strategies differ in cost-effectiveness. At £10,000–30,000 per QALY, the strategy with the greatest probability of being cost-effective is 5% HLA plus IgA tTG; above this range, 1% IgA tTG has the greatest probability of being cost-effective. However, the CEAC does not account for the magnitude of differences between net benefits, which, as reported in *Table 22*, are negligible, with overlapping 95% CrIs.

Table S20 (see *Report Supplementary Material 1*) provides the proportion of time spent in each state for adult women on the strategies of interest. Compared with other pre-test probability strategies with the same serological tests, the 1% IgA EMA strategy has the greatest proportion of time in the CD, gluten-free diet, no-complications state and the least time in the undiagnosed states. Osteoporosis appears to be the complication most patients spend time in; women appear to spend up to four times as much time with this complication as men. The HLA strategies have a greater proportion of time in the CD, gluten-free diet, no-complications state and less time in the undiagnosed states than any IgA EMA strategies. They have almost identical proportions of time in the states across the different pre-test probabilities, with only minor differences between the undiagnosed CD, no-complications state and the undiagnosed CD, osteoporosis state. Overall, cost-effectiveness appears to be mostly driven by time spent in the CD, gluten-free diet, no-complications state; the CD, gluten-free diet, osteoporosis state; and the undiagnosed CD, osteoporosis state.

The ratio of EVPPI to EVPI for each parameter is illustrated in *Figure 21*. As in the population of adult men, the probability of late diagnosis and the sensitivity of the HLA test are important parameters. However, the specificity of the IgA EMA test among adults is also important. The specificity of the HLA test, test cost of IgA tTG and cost of osteoporosis have low influence, and the remaining parameters have almost no influence on results.

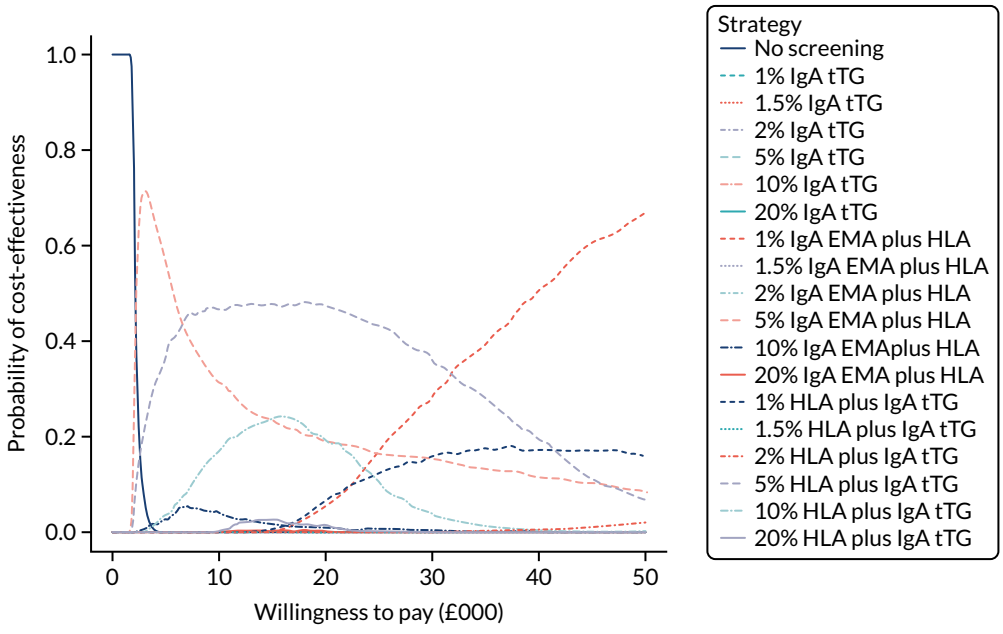

FIGURE 20 Cost-effectiveness acceptability curves for strategies of interest for adult women.

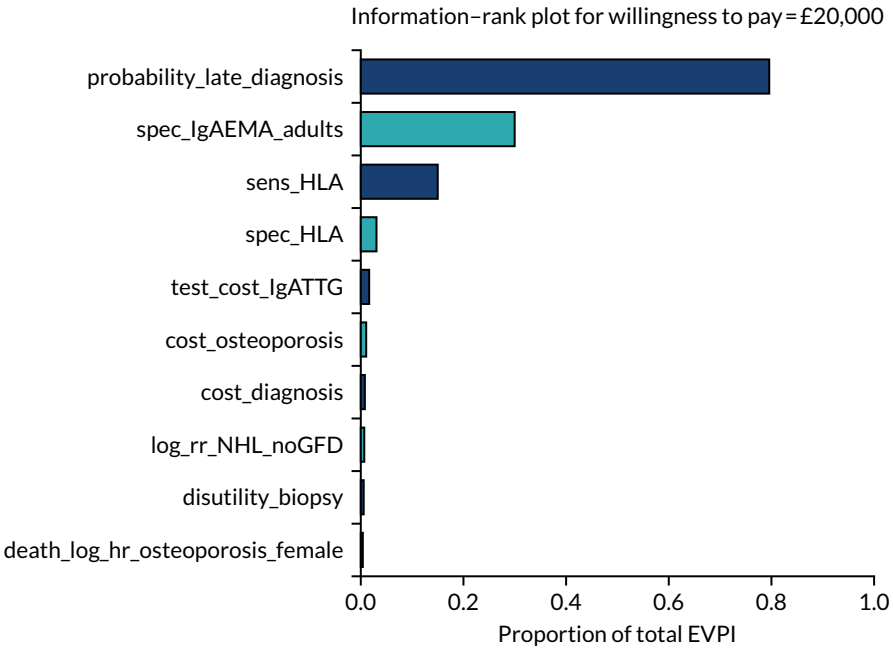

FIGURE 21 Ratio of EVPPI for each parameter to total EVPI for adult women. Only the 10 most influential parameters are included; the remaining parameters have minimal influence on the results. GFD, gluten-free diet; log_rr_NHL_noGFD, log-risk ratio of developing NHL, not on GFD, compared with being on GFD, for coeliac patients; death_log_hr_osteoporosis_female, log-hazard ratio of mortality with osteoporosis, compared with general population, for females; sens, sensitivity; spec, specificity.

The total EVPI and EVPPI for parameter sets of interest are summarised in *Table 21*. The total population EVPI for women is £79.0M, indicating potential value in conducting further research. This is greater than the potential value for men (£25.7M). As with men, the EVPPI for parameter sets indicates that the greatest potential value lies in a study of probabilities of late diagnosis (£68.5M) and on test accuracies (£43M). These values are two to three times greater than the corresponding values for men, suggesting that research should be focused on the adult women population.

Children

Figure 22 plots the incremental net benefit at £20,000 per QALY for risk prediction strategies. Results are similar to those in adults, but uncertainty is greater as the 95% CrIs are wider and, for strategies without HLA, now include 0 (i.e. the strategy is not cost-effective when compared with no screening). *Figure 22* shows that, for the serological tests without HLA, the incremental net benefit at £20,000 per QALY is positive only when the diagnostic indicator sensitivity is > 0.9 or if the specificity is > 0.9 and sensitivity is > 0.8. For the tests including HLA, the incremental net benefit is positive regardless of the accuracy of the diagnostic indicator, except for IgA tTG plus HLA, which requires both sensitivity and specificity of the diagnostic indicator to be > 0.6. Cost-effectiveness is the same if HLA is applied before or after EMA or tTG plus EMA, except when combined with IgA tTG alone, in which case only HLA plus IgA tTG (i.e. IgA tTG as confirmatory test after HLA) is cost-effective, compared with no screening.

Figure 23 plots the probability that each combination of diagnostic indicator sensitivity and specificity is cost-effective for each serological test (i.e. the proportion of simulations that have a positive incremental net benefit, compared with no screening, at various willingness-to-pay thresholds). It shows that the only IgA EMA, IgA tTG plus EMA or IgA tTG strategies with probabilities of > 50% of being cost-effective are those with diagnostic indicator sensitivity of > 0.9 or both specificity and sensitivity of > 0.8. As expected, the combinations with the highest probabilities of being cost-effective are those with a specificity of 0.9 and a sensitivity of 0.9 or 1. The serological tests including HLA have a high probability of being

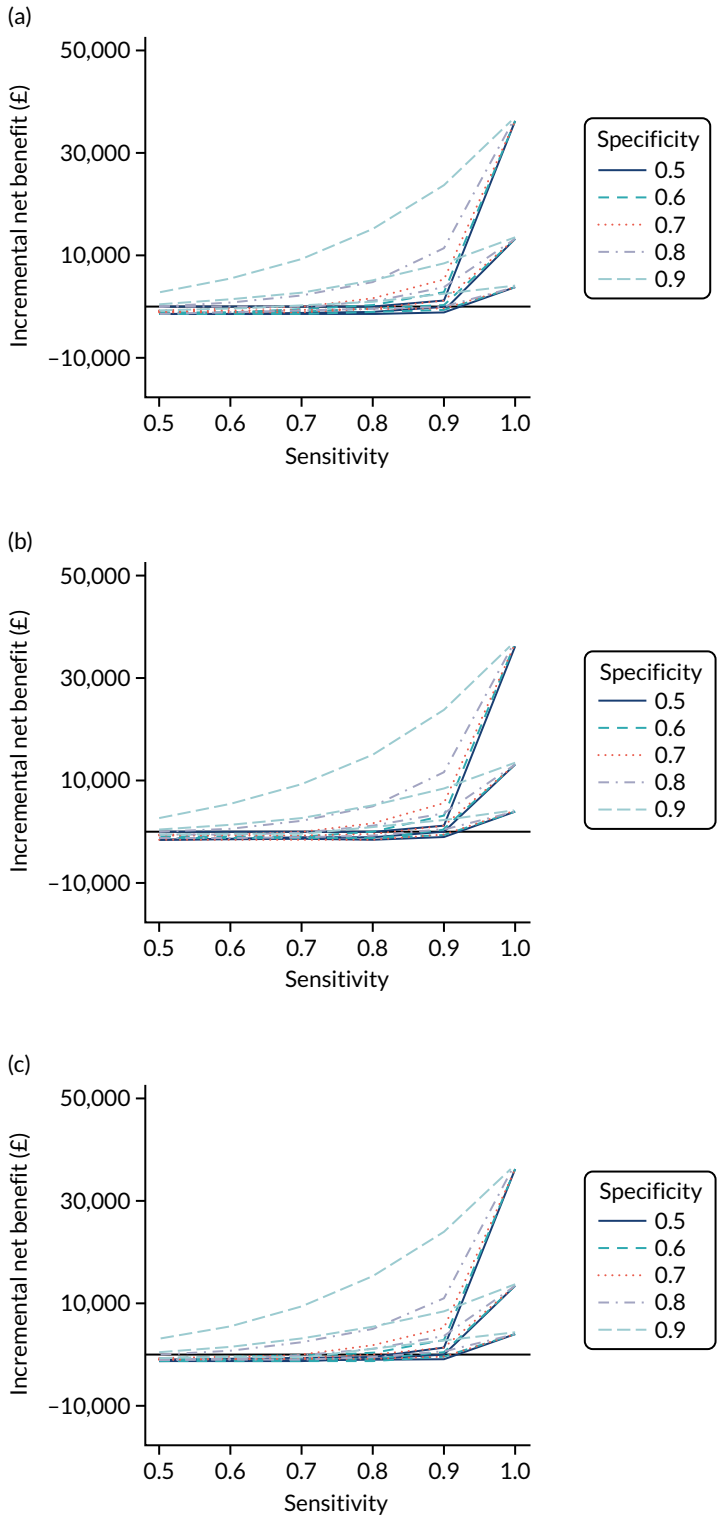

FIGURE 22 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI. (*continued*)

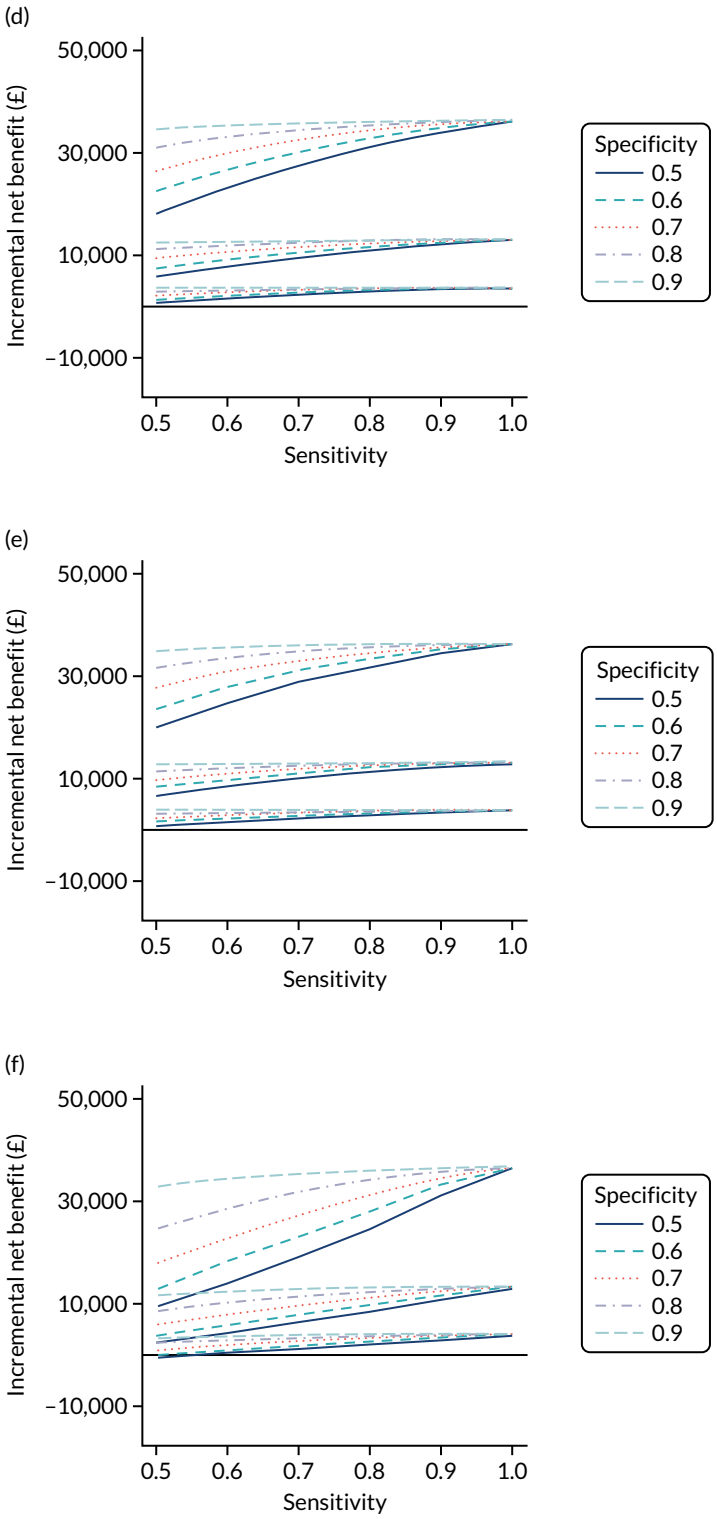

FIGURE 22 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI. (*continued*)

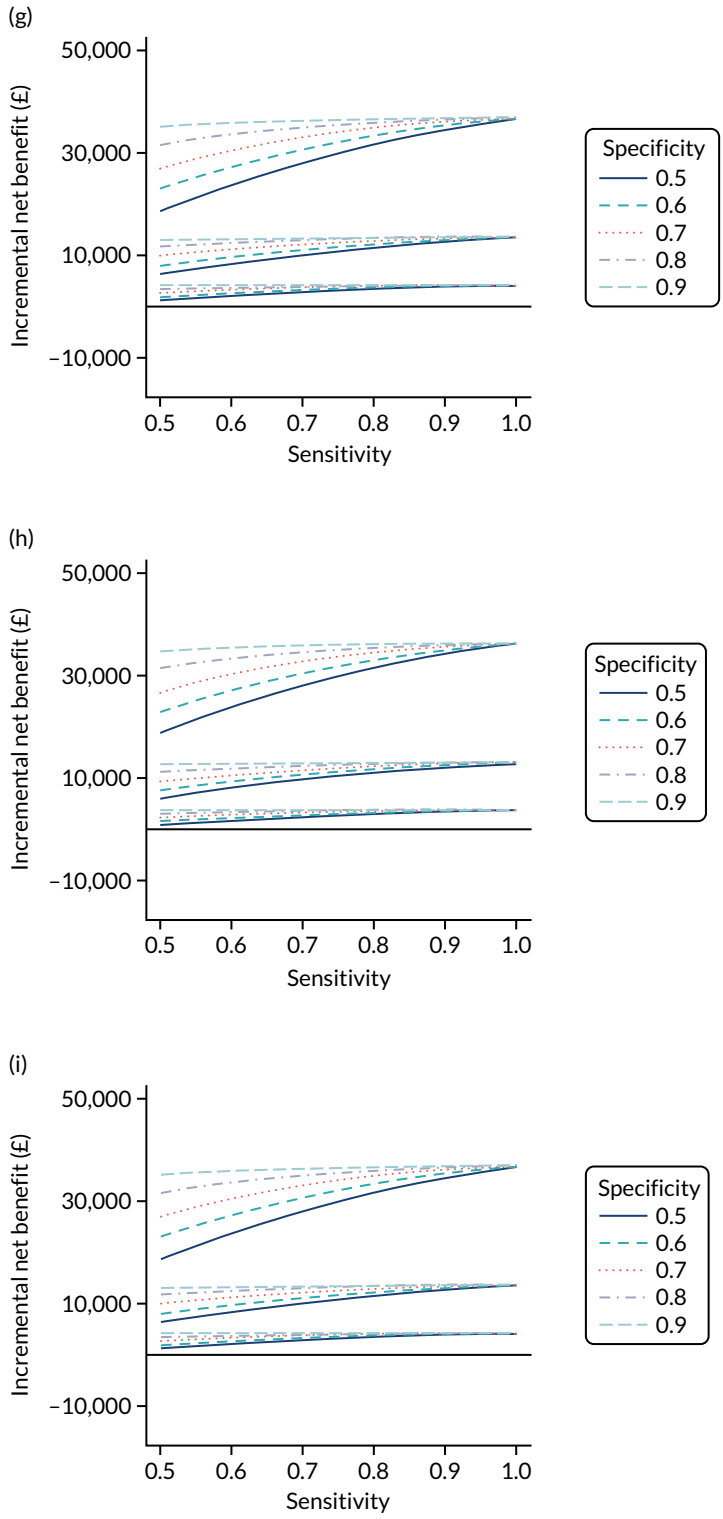

FIGURE 22 Incremental net benefit at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. Note that thick lines indicate the mean and narrow lines indicate the 95% CrI.

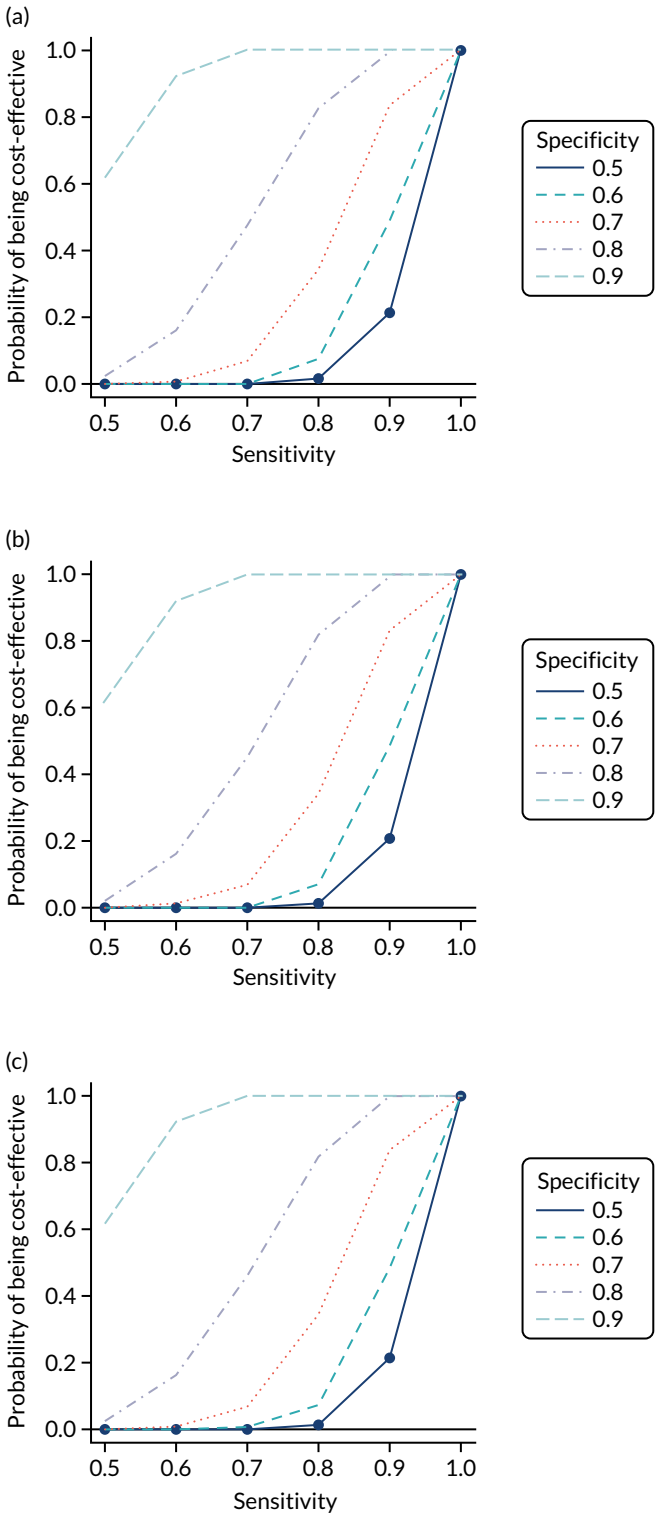

FIGURE 23 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

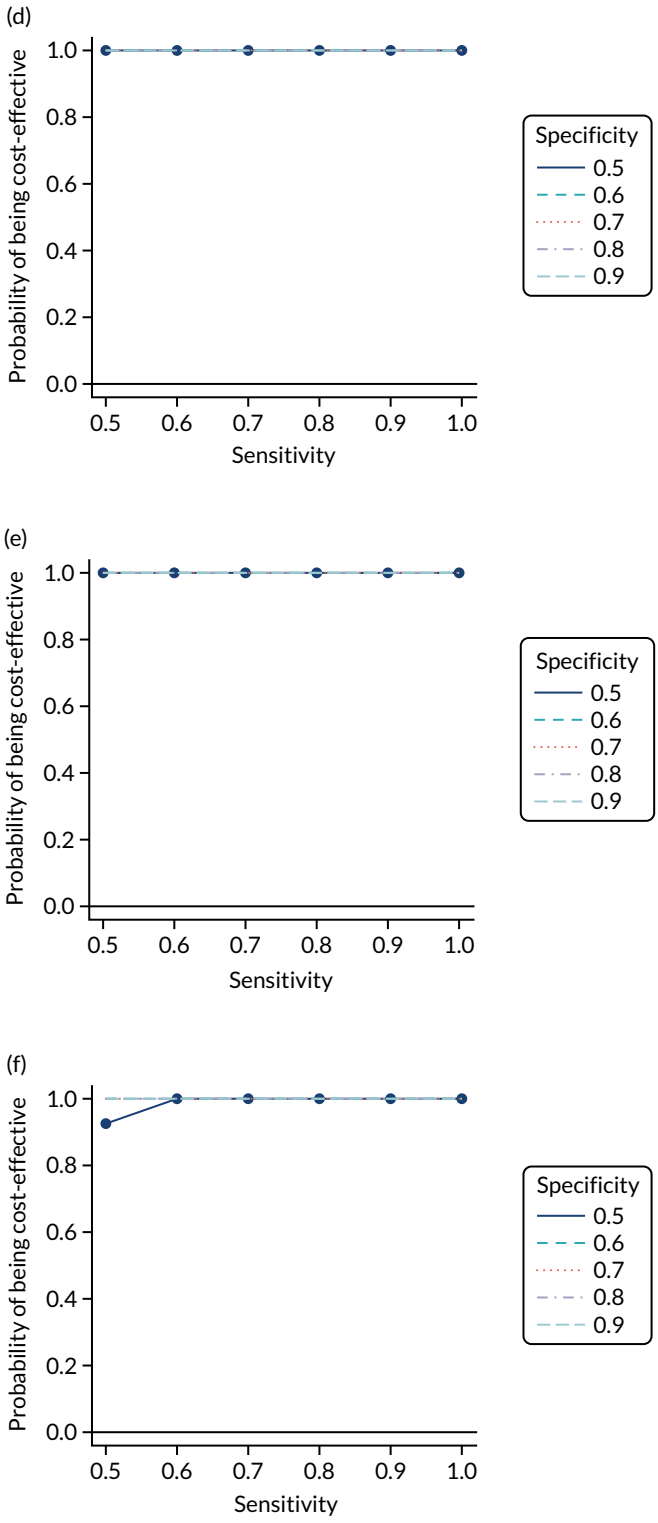

FIGURE 23 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG. (*continued*)

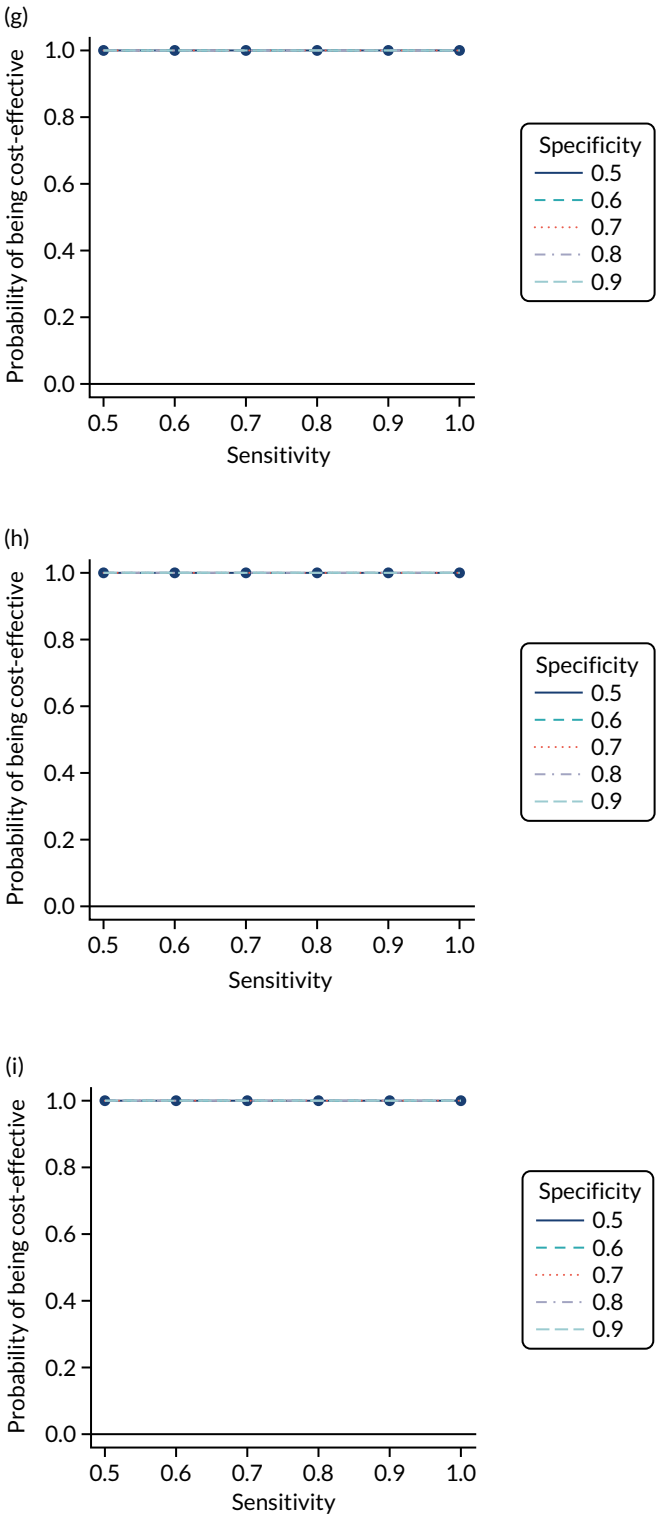

FIGURE 23 Probability of being cost-effective at £20,000 per QALY, compared with no screening, at each combination of sensitivity (*x*-axis) and specificity (line colour) for children. (a) IgA EMA; (b) IgA tTG plus EMA; (c) IgA tTG; (d) IgA EMA plus HLA; (e) IgA tTG plus EMA plus HLA; (f) IgA tTG plus HLA; (g) HLA plus IgA EMA; (h) HLA plus IgA tTG plus EMA; and (i) HLA plus IgA tTG.

cost-effective regardless of the combination of sensitivity and specificity of the risk test. The only exception is IgA tTG plus EMA, which requires a sensitivity of > 0.50 to have a high probability of being cost-effective.

As with the adult population, we selected the testing strategies IgA tTG alone, IgA EMA plus HLA and HLA plus IgA tTG to combine with the various pre-test probabilities listed in *Table 5*. This is justified, as strategies using IgA tTG and IgA EMA have similar incremental net benefits and probabilities of being cost-effective, IgA tTG plus HLA performs worst among strategies with HLA, there is limited difference between IgA tTG plus EMA plus HLA and IgA EMA plus HLA (i.e. not employing tTG), the order in which HLA and EMA tests are conducted has little impact, and HLA plus IgA tTG has high cost-effectiveness and employs a widely available test.

Table 23 shows the estimated costs, QALYs and incremental net benefits, compared with no screening, for each of these strategies of interest. All combinations, apart from pre-test probabilities of 1.5% and 2% with IgA tTG, have a positive incremental net benefit at £20,000 per QALY, compared with no screening. If using only IgA tTG, a pre-test probability of 1% is the most cost-effective strategy (i.e. has greatest incremental net benefit at £20,000 per QALY), with highest costs but also the largest number of QALYs. If using IgA EMA plus HLA or HLA plus IgA tTG, the pre-test probability of 10% is the most cost-effective. As with the adult population, however, the net benefits of all IgA EMA plus HLA and HLA plus IgA tTG strategies are very similar to each other and to 1% IgA tTG, and the 95% CrIs overlap. This indicates little difference between the cost-effectiveness of these strategies, but the differences are greater than they are for adults.

Figure 24 plots the CEACs, which show the probability that each testing strategy is optimal (i.e. has the highest net benefit) at each willingness-to-pay threshold for an additional QALY. This shows that, at any threshold > £5000 per QALY, the strategy with the greatest probability of being cost-effective is 10% HLA plus IgA tTG. This probability is between 60% and 80%, which, although high, does not suggest certainty that any of the IgA EMA plus HLA or HLA plus IgA tTG strategies differ in cost-effectiveness.

Table S21 (see *Report Supplementary Material 1*) provides the proportion of time spent in each state for children on the strategies of interest. Compared with other IgA tTG strategies, the 1% IgA tTG has the greatest proportion of time spent in the CD, gluten-free diet, no-complications state and the least time in the undiagnosed states, and similarly for the 5% HLA strategies compared with other HLA strategies. There is little difference in the proportions of time spent in the undiagnosed, complication states, as most child patients are eventually diagnosed. Time spent in the death state is the same across strategies for this reason. Overall, cost-effectiveness appears to be driven by time spent in the CD, gluten-free diet, no-complications state and the undiagnosed CD, no-complications state.

The total EVPI and EVPPI for parameter sets of interest are summarised in *Table 21*. The total population EVPI is £18.4M, indicating potential value in conducting further research. However, this potential value is less than that for adult men (£25.7M) and adult women (£79.0M). As with adults, the EVPPI is greatest for the probability of late diagnosis (£10.6M) and test accuracies (£7.8M). These are half of the corresponding values for adult men and about six times lower than for adult women, again suggesting that research should be focused on adult women.

The ratio of EVPPI to EVPI for each parameter is illustrated in *Figure 25*. As with the adult population, probability of late diagnosis, disutility of biopsy and specificity of IgA EMA are important parameters. Note that the effect of a gluten-free diet (i.e. being diagnosed with CD) on osteoporosis is picked out as highly influential, and actually its estimated EVPPI is greater than the total EVPI (note that proportion exceeds 1.00). This is due to an algorithm failure. The EVPPI estimated in *Table 21* is based on MLMC methods, whereas the ratios in *Figure 25* are based on generalised additive models, and the latter have been found to be unstable in comparison with the former in the literature.[254]

TABLE 23 Costs, QALYs and incremental net benefits associated with strategies of interest in children. Mean estimates with 95% CIs

Pre-test probability for blood test (%)	Sensitivity	Specificity	Strategy	Mean (95% CI)		
				Costs (£)	QALYs	Incremental net benefit at £20,000 per QALY vs. no screening (£)
No screening				11,746 (10,204 to 12,966)	20.6 (19.18 to 21.6)	0 (0 to 0)
1	1	0	IgA tTG	13,537 (12,558 to 14,637)	21.29 (20.29 to 22.14)	12,203 (3257 to 34,639)
1.5	0.882	0.417	IgA tTG	13,074 (11,577 to 14,280)	20.62 (19.25 to 21.61)	−841 (−1296 to 242)
2	0.807	0.61	IgA tTG	12,914 (11,431 to 14,119)	20.62 (19.27 to 21.62)	−574 (−1074 to 638)
5	0.667	0.872	IgA tTG	12,713 (11,343 to 13,890)	20.71 (19.48 to 21.67)	1290 (−226 to 5072)
10	0.533	0.952	IgA tTG	12,679 (11,477 to 13,793)	20.87 (19.8 to 21.78)	4517 (1002 to 13,401)
20	0.331	0.987	IgA tTG	12,699 (11,686 to 13,797)	21.09 (20.08 to 21.95)	8896 (2610 to 24,765)
1	1	0	IgA EMA plus HLA	13,808 (12,814 to 14,911)	21.32 (20.32 to 22.16)	12,502 (3202 to 35,895)
1.5	0.882	0.417	IgA EMA plus HLA	13,403 (12,418 to 14,497)	21.26 (20.25 to 22.1)	11,577 (3050 to 33,066)
2	0.807	0.61	IgA EMA plus HLA	13,226 (12,242 to 14,325)	21.26 (20.26 to 22.12)	11,878 (3293 to 33,524)
5	0.667	0.872	IgA EMA plus HLA	13,018 (12,030 to 14,117)	21.3 (20.29 to 22.14)	12,872 (3840 to 35,630)
10	0.533	0.952	IgA EMA plus HLA	12,994 (12,003 to 14,103)	21.31 (20.31 to 22.14)	13,085 (3919 to 36,248)
20	0.331	0.987	IgA EMA plus HLA	13,034 (12,033 to 14,133)	21.31 (20.31 to 22.15)	13,040 (3820 to 36,375)
1	1	0	HLA plus IgA tTG	13,800 (12,808 to 14,901)	21.32 (20.32 to 22.16)	12,509 (3210 to 35,884)
1.5	0.882	0.417	HLA plus IgA tTG	13,397 (12,416 to 14,492)	21.26 (20.26 to 22.1)	11,618 (3029 to 33,293)
2	0.807	0.61	HLA plus IgA tTG	13,221 (12,241 to 14,321)	21.26 (20.27 to 22.12)	11,914 (3273 to 33,675)
5	0.667	0.872	HLA plus IgA tTG	13,014 (12,027 to 14,114)	21.3 (20.29 to 22.14)	12,885 (3844 to 35,682)
10	0.533	0.952	HLA plus IgA tTG	12,991 (11,998 to 14,100)	21.31 (20.31 to 22.14)	13,090 (3929 to 36,260)
20	0.331	0.987	HLA plus IgA tTG	13,032 (12,029 to 14,132)	21.31 (20.31 to 22.15)	13,042 (3835 to 36,372)

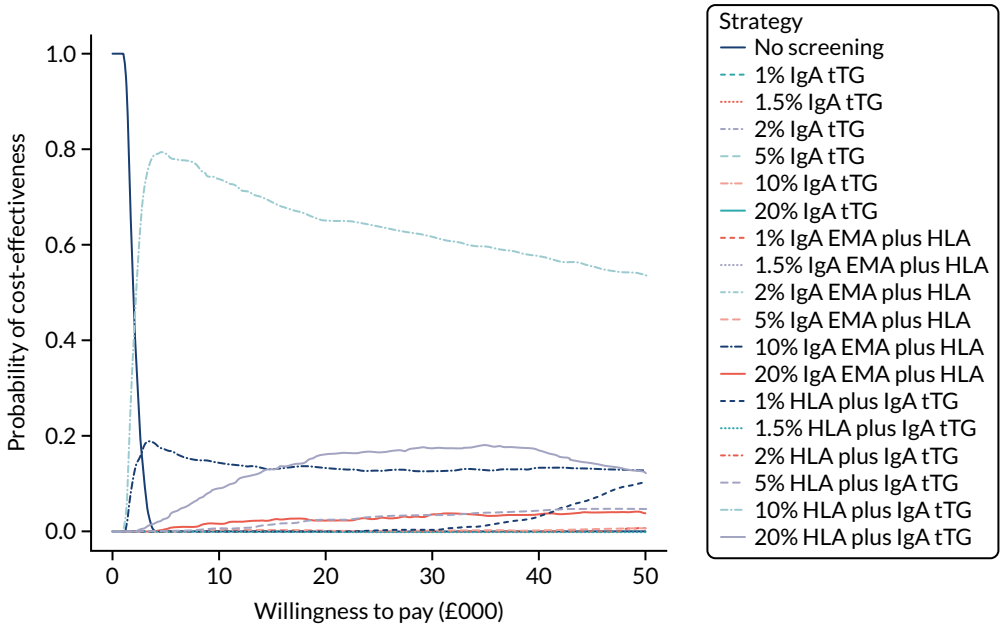

FIGURE 24 Cost-effectiveness acceptability curves for strategies of interest for children.

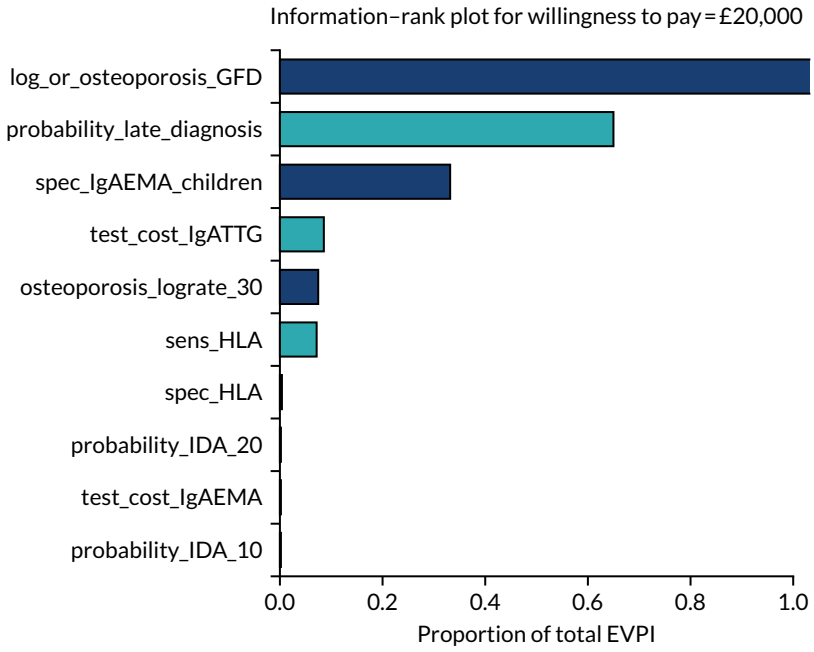

FIGURE 25 Ratio of EVPPI for each parameter to total EVPI for children. Only the 10 most influential parameters are included. Note that log_or_osteoporosis_GFD is high, but this is due to numerical failure of the algorithm. The remaining parameters have minimal influence on the results. GFD, gluten-free diet; log_or_osteoporosis_GFD, log-odds ratio of developing osteoporosis on GFD, compared with not on GFD, for coeliac patients; probability_IDA_20, prevalence of IDA at age 20 years; probability_IDA_10, prevalence of IDA at age 10 years; sens, sensitivity; spec, specificity.

Chapter 9 Discussion

Statement of principal findings

In *Chapter 3*, we identified diagnostic indicators and calculated summary estimates for their accuracy in identifying individuals at high risk of CD. None of the identified diagnostic indicators alone had good sensitivity for detecting CD; however, some showed promise in helping to identify patients who should be offered serological testing. The estimated PPVs for migraine, family history of CD, anaemia, type 1 diabetes, osteoporosis and chronic liver disease were all > 2%, with 95% CIs lying entirely above the population prevalence of 1%. These results suggest that individuals with these conditions are twice as likely to have CD as the general population. There was too little evidence to show an increased risk of CD among individuals with systemic lupus erythematosus or multiple sclerosis. Dermatitis herpetiformis showed the highest diagnostic accuracy; however, because dermatitis herpetiformis is rare and treatment is a gluten-free diet even in the absence of a CD diagnosis,[258] it is unlikely to be helpful as a diagnostic indicator. GI symptoms showed poor diagnostic ability, whereas individuals with a first-degree relative with CD had a risk of CD that was three times higher than that of the general population.

In *Chapter 4*, we developed prediction models for children, women and men. The final models included 24, 24 and 21 predictors, respectively. For children, having type 1 diabetes, Turner syndrome, IgA deficiency or a first-degree relative with CD were estimated to be the strongest predictors (i.e. had the highest estimated coefficients). For women and men, the strongest predictors were having a first-degree relative with CD, and anaemia. In the development data set, the model showed good discrimination between patients with and patients without CD, as demonstrated by high *c*-statistics: 0.84 (95% CI 0.83 to 0.84) for children, 0.77 (95% CI 0.77 to 0.78) for women and 0.81 (95% CI 0.81 to 0.82) for men. The model discriminated less well between patients with and patients without CD in the external validation data set, in which the *c*-statistics reduced to 0.60 for children, 0.55 for women and 0.62 for men. However, the predictor first-degree relative with CD was not recorded in the validation data set, which was one of the most important predictors, leading to an underestimation of model performance in this data set. The models were poorly calibrated and tended to overestimate the risk of having CD in all three groups in the development data set and the validation data set. The models suggest that individuals with any of the selected predictors have an increased risk of CD of > 50% and thus warrant testing for CD.

In *Chapter 5*, we estimated the diagnostic accuracy of the most commonly used serological tests for CD: IgA tTG and IgA EMA. IgA tTG was found to have a summary sensitivity of 91% (95% CI 87% to 93%, threshold: 15 U/ml) among adults and 98% (95% CI 91% to 99%, threshold: 20 U/ml) among children, based on five[90,100,110,175,176] and six[121,134,136,140,141,146] studies, respectively. IgA tTG specificity was estimated at 87% (95% CI 84% to 90%) among adults and 70% (95% CI 39% to 90%) among children. IgA EMA showed a sensitivity of 88% (95% CI 75% to 95%, threshold: 1 : 5) among adults and 95% (95% CI 89% to 97%, threshold: 1 : 10) among children, based on five studies each. The specificity of IgA EMA was 99.6% (95% CI 92% to 100%, threshold: 1 : 5) among adults and 94% (95% CI 85% to 98%, threshold: 1 : 10) among children. To select estimates to inform the economic model, we restricted our analysis to studies that had evaluated the two main serological tests of interest (IgA tTG and IgA EMA, alone and in combination) at the same threshold. This was to ensure that estimates used in the economic model were directly comparable. None of the studies that evaluated both tests alone

and in combination reported accuracy estimates for the same thresholds. We therefore selected the studies that were judged to be at the lowest risk of bias and that had the largest sample sizes. This means that evidence to inform the economic model is derived from two studies, one with adults and one with children, despite identifying > 100 studies that evaluated the accuracy of serological tests for CD. For both adults and children, IgA tTG had the highest sensitivity, although estimates for children were very similar, and EMA had the highest specificity. There was little improvement in either sensitivity or specificity when the tests were used in combination. Despite thresholds being the same as those used in the meta-analyses for the individual tTG and EMA tests, there were minor differences between estimates from these studies and summary estimates when all studies that reported at the same thresholds were pooled.

In *Chapter 6*, we estimated the accuracy of *HLA-DQ2* and/or *-DQ8* genotyping to diagnose CD. Summary sensitivity was very high, at 99% (95% CI 83% to 100%), and specificity was 56% (95% CI 50% to 61%). The high sensitivity suggests that HLA genotyping would be a useful test to rule out CD. However, because of the low specificity, this test needs to be used in combination with other tests to diagnose CD.

In *Chapter 7*, we used collaborative work with patients and an online survey to identify the level of diagnostic certainty people want to have for CD testing and starting treatment. Survey respondents wanted to be a median of 66% (IQR 33–90%) certain of the blood test result before starting a gluten-free diet if they were asked to imagine that they had CD symptoms. Without symptoms, respondents wanted to be more certain of the blood test result before committing to a gluten-free diet: median 90% (IQR 66–99%). However, a higher proportion of respondents opted to wait for a confirmation biopsy, if given the option, instead of starting a gluten-free diet immediately, even if a hypothetical blood test gave 75–90% certainty. The free-text answers revealed no barriers to a blood test. Reasons for opting for a confirmation biopsy were to feel more confident about the diagnosis or to get an official diagnosis. Barriers to a biopsy were that it was invasive and unpleasant. Waiting times did not emerge as an important barrier for having a biopsy. There was large variation in attitudes towards following a gluten-free diet. Some respondents were willing to start the diet only with high risk or great certainty of having CD, whereas others were happy to try it without having a diagnosis or when at very low risk of having CD.

The findings from all previous chapters informed the cost-effectiveness analysis presented in *Chapter 8*. We used a decision tree and discrete-time cohort Markov model to compare the cost-effectiveness of case-finding strategies at different levels of pre-test probability separately for men, women and children. For adult men and women, and using serological testing alone, a 1% pre-test probability (equivalent to population screening) had the highest net benefit at £20,000 per QALY, with an incremental net benefit, relative to no screening, of £24,331 (95% CrI £5080 to £56,493) for men and £24,382 (95% CrI £4829 to £59,154) for women. Serological tests (IgA EMA and IgA tTG) had similar cost-effectiveness and there was limited benefit to including both EMA and tTG. The 1% IgA tTG strategy had a nearly identical net benefit to, and a 95% CrI that overlapped with, those of strategies using both HLA and serological testing. Moreover, none of the strategies had a probability of being the most cost-effective of > 60% for men or > 50% for women, suggesting limited certainty that they differ in cost-effectiveness. Using IgA tTG alone with a 1% pre-test probability or any HLA plus IgA tTG strategy represents a practical combination of tests, as IgA tTG is routinely available in UK laboratories, is easier to interpret and also provides some indication of reversal of mucosal damage.[247]

The 95% CrIs on net QALYs, costs and net benefits were very wide and differences between optimal strategies were not substantial. Our model was limited by a lack of data on the impact of gluten-free diet on rates of osteoporosis and NHL among coeliac patients, and on the routine diagnosis of CD regardless of screening. We used a value-of-information analysis to identify the most 'important' uncertainties, defined by their extent of uncertainty and impact on model conclusions. This identified the probability of being eventually diagnosed regardless of screening (i.e. probability of a late diagnosis) as the most important uncertainty for both adult men and women. For men, the sensitivity of HLA,

the accuracy of IgA EMA and the impact of a gluten-free diet on the chance of developing osteoporosis among coeliac patients were also important uncertainties. For women, the only other important uncertainties were the specificity of IgA EMA and the sensitivity of HLA.

For children, a pre-test probability of 10% with HLA plus IgA tTG had the greatest net benefit at £20,000 per QALY, with an incremental net benefit of £13,090 (95% CrI £3929 to £36,260), relative to no screening. This also had a probability of 60–80% of being cost-effective at a willingness-to-pay threshold of > £10,000 per QALY. As with adults, the 95% CrIs were very wide, indicating substantial uncertainty in our results. The 20% HLA plus IgA tTG- and 2% IgA tTG-alone strategies also had probabilities of about 20% of being the most cost-effective. The greatest and most influential uncertainties for children, as identified by a value-of-information analysis, were the probability of being eventually diagnosed regardless of screening, and the specificity of IgA EMA.

For adults, the greatest difference between strategies was between the time in the undiagnosed CD, osteoporosis state and the time in the CD, gluten-free diet, no-complications state. This was supported by the EVPPI analysis, which found the probability of late diagnosis (i.e. the parameter that drives time in undiagnosed states) to be the most influential. For children, the time in the CD, gluten-free diet, no-complications state was, again, indicated to be important by both time in states and EVPPI. The effect of a gluten-free diet on osteoporosis rates was identified as important by the EVPPI analysis for children, which is likely to be explained by their greater time to benefit from a gluten-free diet and avoid subsequent osteoporosis.

The total population EVPI was £25.7M for men, £79.0M for women and £18.4M for children, indicating substantial potential value of further research. The EVPPI analyses for adults indicated up to three times as much value among women as men. However, in both populations there was substantial potential value in research on the probability of late diagnosis and the accuracy of serological and genetic tests. The population EVPPI estimates for children were lower than for adult men or women, but probability of late diagnosis and test accuracies again came out as most important for future research. To prioritise optimal further research, expected value of sample information should be calculated for suggested research designs.[259]

Strengths and limitations

A key strength of the systematic reviews and meta-analyses was that we applied a robust methodological approach following internationally recognised systematic review guidance. We used sensitive literature search strategies, and study selection was performed by at least two reviewers independently. Data extraction was performed by one reviewer and checked by a second to ensure accuracy and completeness. We conducted detailed risk-of-bias assessments using a validated tool.[28] We applied stringent inclusion criteria to minimise bias. Syntheses of studies were carried out in line with Cochrane-recommended methods and sensitivity analyses were performed to explore heterogeneity.[22,23]

For the diagnostic indicator (see *Chapter 3*) and accuracy of serological test reviews (see *Chapter 5*), the interpretation of meta-analyses results was limited by the substantial heterogeneity between the included studies, and most included studies were judged to be at high risk of bias. We investigated sources of variability in the diagnostic indicator review by performing stratified meta-analyses by age group, definition of CD and study design; only a small minority of diagnostic indicators were reported by enough studies to perform these analyses. Finally, we limited our review to diagnostic indicators that were reported by at least five studies; therefore, we may have missed other promising diagnostic indicators that are evaluated less often. Our broad inclusion criteria, such that any diagnostic indicator evaluated in an appropriately designed study was eligible for inclusion, mean that we had the potential to identify diagnostic indicators not currently recommended by guidelines.

In the review of the diagnostic accuracy of serological tests, a wide variety of thresholds for test positivity were reported across studies, with some not reporting the threshold at all. When threshold units differed between assays, we assumed that they represented the same arbitrary units and were comparable. However, as they do not measure absolute amounts of antibodies, there may be slight variation between different commercial assays and between laboratories. There was substantial variation in CD prevalence between studies, probably due to differences in patient recruitment. Some studies excluded patients with IgA deficiencies whereas others did not, which may have affected the accuracy estimates for tests that detected the presence of IgA in serum samples. Sources of heterogeneity were explored through sensitivity analyses; summary results were relatively robust to a number of exclusions. Very few studies provided direct comparison of the serological tests, and those that did reported accuracy at different thresholds. This means that, despite the review including 113 studies, estimates used for the economic model were based on single studies with adults and children. We considered it more appropriate to have directly comparable estimates of the accuracy of IgA EMA and IgA tTG, alone and in combination, than to take the estimates from the meta-analyses as different studies contributed to these.

A key strength of our prediction models (see *Chapter 4*) is that we preselected diagnostic indicators to consider in the model based on a review of the literature, as well as current practice guidelines and discussions with clinical experts. We avoided using traditional approaches for model selection, such as stepwise selection, which aim to include only the most significant predictors in a model. Disadvantages of this method are instability of the selection, biased testimation of coefficients (estimation bias), misspecification of variability and exaggeration of *p*-values.[44] We performed a second step in variable selection using elastic net regression and bootstrapping, to exclude predictors that have a very small or uncertain effect on the prediction of CD. The elastic net method is a modern approach to variable selection that uses shrinkage, which optimises the variance (precision) and bias (accuracy) trade-off. It minimises overfitting on development data, thereby creating a more robust model for use in the future. Another important strength of the models is that they were developed in a large primary care data set using robust definitions of predictors and were externally validated in another large UK primary care data set. We used the *International Classification of Primary Care* definitions where available.[52] The corresponding code lists were taken from publications when possible, and all code lists were checked by at least two clinicians.[260] This makes the model more applicable and generalisable, as the model is intended to be used in the primary care setting and GPs have access to the information needed for the model during consultation.

A major limitation of the prediction models is that, as CD is underdiagnosed, it is also under-reported in the CPRD. The prevalence of CD in both primary care data sets used in *Chapter 5* was around 0.1%, which is 10 times lower than the estimated population prevalence in the UK. As a result, we may have selected undiagnosed CD patients in our control group, which could have led to an underestimation of the importance of indicators. To reduce the number of undiagnosed CD patients in the control group, we excluded patients with related conditions, such as dermatitis herpetiformis, and people receiving gluten-free prescriptions. What is more problematic is that diagnosed CD patients may have different characteristics from undiagnosed CD patients. We were, therefore, more likely to confirm predictors that are already in the guidelines because those indicators currently prompt testing. Different indicators may be important for undiagnosed CD patients; however, it was not possible to investigate this in this data sets. The results from the diagnostic indicator review were considered more robust for individual diagnostic indicators as we accepted only studies in which all participants were tested for CD; this may explain why some of the indicators identified by our review, such as migraine, were not found to be important indicators in the prediction models. Our recommendations on who should be tested are, therefore, based on both the results of the indicator review and the results of the prediction models.

A further limitation of using routine CPRD data to develop the prediction models is that we were able to investigate only diagnostic indicators that were recorded by GPs. We were, therefore, not able to evaluate some potentially important indicators, such as dental enamel defects, as these are not routinely recorded in primary care. We also relied on accurate recording of indicators by GPs and reporting by

patients; non-specific symptoms such as GI symptoms and fatigue are likely to be under-reported and so cannot be fully evaluated using primary care data. Although we used large sample sizes, some indicators, such as Williams–Beuren syndrome, were too rare to be included in our models. This is a limitation of the model because these indicators are important according to several CD guidelines.[9–11]

A further limitation in the study design for the prediction model is that we used a nested case–control design. A cohort design is recommended for prediction modelling and is necessary for reliable estimations of model calibration because it compares the indicators with the observed prevalence. We artificially inflated the control group to recreate a CD prevalence similar to the general population, which allowed us to estimate calibration statistics. This enabled us to calculate and compare all performance measures. This method may have inflated any bias present in the original control group and might explain the poor calibration shown in our models. However, we believe this risk was low because the control group had a large sample size (> 80,000 patients, large enough to reflect variation in all indicators) and controls had been randomly selected from a sample that is largely representative of the UK. We recreated a cohort with the estimated population prevalence of CD (1%), not the prevalence observed in the CPRD (0.1%), which is lower than the actual population prevalence as CD is underdiagnosed. Another limitation of this approach is that we have no information about the characteristics of those with CD who have not been diagnosed and therefore had to assume that they are similar to the characteristics of those who are diagnosed, which is likely to be incorrect.

We used an innovative form of patient involvement in this project that directly influenced our economic model. The survey (see *Chapter 7*) was developed in collaboration with CD patients and tested by people with and people without knowledge of CD. We developed videos to make the information more accessible. The qualitative analyses of free-text answers provided context and helped in interpreting the multiple-choice answers.

Although we used multiple routes of promoting the survey to get a variety of people to fill it out, the sample was not representative of the UK (the majority were highly educated white women), which is a common problem with online surveys. Another limitation was that we recruited participants online and the survey was available only in an online format, which may have excluded those who do not have access to internet or do not use social media. The free-text answers revealed that some respondents misunderstood questions, which may have skewed the results. We may have overestimated the adherence to a gluten-free diet because of non-responder biases, that is those with 'poor adherence' to a gluten-free diet may be less likely to respond to a questionnaire.

The cost-effectiveness analysis was based on a state-of-the-art cohort Markov model. We used the CPRD analysis and clinical advice to identify the most important comorbidities of CD, namely osteoporosis and NHL. The model is fully probabilistic, which means that it avoids assuming that uncertain parameters are fixed. The uncertainty in epidemiological and utility parameters was modelled with statistical distributions and this uncertainty was propagated to the final costs, QALYs and net benefits. We went further and conducted value-of-information analyses to identify the most influential uncertain parameters and quantify the value in further research. Furthermore, the model was implemented in the R statistical programming language and optimised using C/C±, which has extensive benefits in flexibility, transparency and efficiency over the more usual Microsoft Excel.

There are several important limitations of the cost-effectiveness analysis. The Markov model structure was a simplification of CD, for example not modelling a difference between symptomatic and asymptomatic CD or allowing patients to have osteoporosis and NHL. Using a cohort modelling approach did not permit modelling of individuals; thus, we modelled an average adult male, adult female and child with CD, rather than a more granular exploration of types of patients. A full individual-level model informed by the CPRD and including more of the indicators identified in *Chapters 3* and *4* is possible. However, this would also require further research on state costs and utilities, and the impact of a gluten-free diet, none of which are guaranteed to have high-quality data, and may not lead to different recommendations.[261]

The data informing our selected model also had limitations. All uncertainties regarding test accuracy from *Chapters 5* and *6* carry through to the cost-effectiveness model. The costs of the IgA EMA, IgA tTG and HLA tests were uncertain; we informed these through quotations provided by laboratories affiliated with our team, but found them to vary even within this small sample. The CPRD analysis could estimate the prevalences of osteoporosis, NHL and IDA in a diagnosed CD cohort only, so the initial prevalences in the undiagnosed CD cohort were assumed to be the same as those of the newly diagnosed CD cohort. However, the prevalences eventually diverge because of the different rates of developing osteoporosis and NHL in diagnosed and undiagnosed CD cohorts. Evidence on routine diagnosis of CD was limited, so we relied on a survey on the duration of symptoms prior to diagnosis.[231] This is problematic, as it considers only patients who are eventually diagnosed and is estimating time from symptoms rather than time from developing CD, thus biasing towards lower times to diagnosis. In our model, we also assumed that time to eventual diagnosis is unaffected by an initial false-negative result from the screening programme; bias could be towards lower times to diagnosis if screening leads to greater awareness of CD or towards longer times if the negative result gives a patient a belief that they do not have CD.

The benefit of a gluten-free diet, in terms of either quality-of-life improvements or reduced rates of complications, was uncertain. Unlike the NICE 2015 model,[193] our model does not distinguish between people with diagnosed CD following a gluten-free diet and people with diagnosed CD not following a gluten-free diet. This is because there are many methodological challenges associated with assessing dietary adherence and a lack of reliable data on the health impacts of following a gluten-free diet or not. Reported gluten-free diet adherence rates vary substantially depending on how adherence is measured and the population studied.[214] Violato *et al.*[231] reported a coefficient for the impact on quality of life of not adhering to a gluten-free diet of −0.14 (95% CI −0.31 to 0.03), compared with adhering all the time.[214] However, we could not use this without a reliable estimate for adherence.

Based on our survey of patients (see *Chapter 7*), we assumed that a confirmatory biopsy would be needed for patients with post-test probabilities of < 90%. This would lead to roughly 70% of patients having a confirmatory biopsy, in accordance with recent research indicating high diagnostic accuracy of tests alone.[70,89,220,221] In all cases of data uncertainty, we varied parameters and propagated uncertainty to the probabilistic results; this perhaps explains the lower probabilities that our optimal strategies were the most cost-effective. A further limitation of our analysis is that we did not consider the capital cost of laboratories across the UK having to establish capacity for IgA EMA or HLA testing. This was considered in the NICE model, which found the results to be insensitive to the inclusion of capital costs.[193] Furthermore, when not including HLA testing, our analyses did not favour IgA EMA or IgA tTG, or a combination thereof. With HLA testing, we found that IgA EMA plus HLA performed similarly to IgA tTG plus EMA plus HLA, meaning that it would be necessary to ensure capacity only for IgA EMA and HLA.

A further limitation of the economic analysis is that the model used the EQ-5D measure of quality of life to capture the effect on quality of life of following a gluten-free diet, which showed no effect, so the model assumes that following the diet causes no disutility. However, the EQ-5D is a very crude measure and does not capture the difficulty of following a strict lifelong diet and its social implications. The CD-QOL (part of the survey in *Chapter 7*) showed that quality of life among CD patients was mainly affected by CD-related limitations and health concerns. However, it is not currently possible to translate results from the CD-QOL to QALYs, making it impossible to use this tool to quantify quality of life in the model.

Finally, a limitation of the serological test accuracy review (see *Chapter 5*) and the economic models (see *Chapter 8*) is that we assumed a 100% accuracy of the biopsy procedure by treating it as a gold standard. No diagnostic procedure is 100% accurate; in clinical practice, the diagnosis of CD relies on a combination of clinical, serological and histopathological findings. There are many potential histopathological mimics that can cause false-positive biopsy results if CD serology is not taken

into account, such as infections, other bowel diseases such as peptic ulcer disease or IBS, and certain medications.[11] The correct orientation and cutting procedure are essential for appropriate interpretation of histopathological findings.[10,11] Detecting mucosal architectural changes is further complicated by the fact that CD does not necessarily affect all parts of the small bowel, and the severity of coeliac lesions can vary between areas.[262] Thus, pathological findings in CD can be patchy, and multiple biopsies are needed to diagnose CD.[263] As a result, interobserver variability is high for the interpretation of biopsy results.[10]

Comparison with other studies

Our estimates of the probability of CD for people with certain risk conditions, compared with the general population, are in agreement with previous reports on the prevalence of CD among individuals with those conditions. Meta-analyses estimated the prevalence of CD to be 3–16% among people with type 1 diabetes,[264] 1.6–3.8% (95% CIs) in studies that measured CD by serological tests only and 2.3–4.5% in studies that included biopsy-proven CD patients among people with IBS,[265] 2.6–3.9% among people with IDA,[33] 1.6–2.6% among people with epilepsy,[266] 1.4–3.5% among women with infertility,[267] 1.3–1.9% among people with autoimmune thyroid disease,[268] 1–7% among people with raised liver enzymes[269] and 1.1–2.0% among people with osteoporosis.[270] A meta-analysis of nine studies found a pooled odds ratio of 1.7–2.7 for CD among individuals with psoriasis, compared with those without psoriasis,[271] and another meta-analysis found a 2.2–7.0 relative risk of CD among patients with inflammatory bowel disease compared with controls.[272] A meta-analysis of 40 studies found that the prevalence of CD among children with migraine-like headaches is 1.5–3.7 times higher than in the general population, but no evidence was reported on adult populations.[273] Our analysis showed a similar increased risk of 2.8-fold, including one study with an adult population that showed similar results.[274]

We found a lower risk than other studies of CD among people with a family history of CD. A meta-analysis of 54 studies showed that the prevalence of CD is 6.3–8.8 times higher among first-degree relatives and 1.3–3.8 times higher among second-degree relatives than in the general population,[275] whereas we found a risk of 1.3 times higher among people with a family history of CD. Only six of our included studies focused specifically on first-degree relatives; the other six included second-degree relatives or did not specify, which can partly explain our lower estimate. When restricting our analysis to first-degree relatives, we estimated the PPV at 1.3–7.2%. Finally, some studies included as few as two individuals with a family history of CD and six individuals with CD in their study population,[276,277] which is likely to have attenuated the estimated association as well.

Small differences between our results in *Chapter 4* and results from previous meta-analyses can be explained by our stringent inclusion criteria. Most studies that used routinely collected data were excluded from our review because, in these studies, patients without a code for CD are assumed to not have the disease. This is problematic because CD is known to be underdiagnosed. Small differences between our estimates of PPV and estimates from meta-analyses of prevalence may also be explained by the fact that we included only studies that allowed estimation of both sensitivity and specificity (which requires some study participants to not have the diagnostic indicator).

To our knowledge, few previous studies have developed prediction models for CD and none has based the prediction rules on symptoms and risk factors alone. Genetic risk models have been developed using HLA and non-HLA variants as predictors of CD. A simple count model that included 10 non-HLA genes on top of the usual HLA risk genes showed better classification than HLA risk genes alone.[278] The same authors further improved their model by increasing the number of non-HLA genes to 57. This model showed good discrimination, with a *c*-statistic of 0.85 (compared with 0.82 for HLA only).[279] These models can help with assessing risk in at-risk groups, but these genetic tests are not readily available to GPs. Our model performed well in the development data set, in which the *c*-statistic

ranged from 0.76 for women to 0.82 for children, which is in the same range as the Framingham Risk Score for coronary heart disease (*c*-statistic of 0.8), which is clinically useful.[280] Other examples of prediction rules that are in use in primary care are the QCancer® scores (ClinRisk Ltd, Leeds, UK), which showed good discrimination, with *c*-statistics ranging from 0.73 to 0.91 for different types of cancer among women[281] and from 0.82 to 0.94 for different types of cancer among men.[282]

Existing evidence on the accuracy of serology for diagnosing CD is mixed. Previous systematic reviews of the accuracy of serological testing for diagnosing CD suggest that the tests are highly sensitive and specific among both adults and children.[12–15] These systematic reviews, however, are out of date and/or have methodological limitations, including issues with the search strategy, how study quality was assessed and how results were synthesised. All reviews included case–control design studies, which have been shown to overestimate test accuracy measures, compared with cohort designs.[68] Rostom *et al.*[13] stratified their analyses by age, test and substrate. The summary sensitivity and specificity of IgA tTG (human recombinant) and IgA EMA tests were > 90% across all age groups. Giersiepen *et al.*[12] conducted a systematic review of antibody test accuracy among children. Meta-analyses were not performed because of between-study heterogeneity; the sensitivity and specificity ranged from 13% to 100% and from 78% to 100%, respectively, for the IgA tTG test and from 83% to 100% and from 95% to 100%, respectively, for the IgA EMA test. Schyum and Rumessen[14] carried out a systematic review of serological test accuracy among adults. Study data were not meta-analysed, but the median sensitivity and specificity were estimated to be 93% and 95%, respectively, for the IgA tTG test and 84% and 100%, respectively, for the IgA EMA test. van der Windt *et al.*[15] estimated serological test accuracy among adults presenting to primary care with abdominal symptoms. The summary sensitivity and specificity were 89% and 98%, respectively, for IgA tTG and 90% and 99%, respectively, for IgA EMA. The sensitivity and specificity estimates for IgA tTG and IgA EMA in our review (see *Chapter 5*) were slightly lower than in previous reviews. Inclusion of case–control studies may have inflated previous accuracy estimates. Finally, a meta-analysis of six studies investigated the accuracy of *HLA-DQ2* and *-DQ8* genotyping for the detection of CD and found a pooled sensitivity of 97–99% and specificity of 41–48%,[283] compared with 99% and 56%, respectively, in *Chapter 6*.

Our findings that IgA EMA, IgA tTG and HLA testing, alone or in combination, of at-risk patients is cost-effective, compared with no screening, are consistent with previously published models. These models used a similar framework of decision trees and Markov models, and most were in the US setting. For example, among patients with IBS symptoms, Main and Ladabaum[196] found tTG to be cost-effective at US$50,000 per QALY gained if pre-test probability was 2%, and found it cost-effective at US$100,000 per QALY gained if pre-test probability was 1.1%. Shamir *et al.*[198] used a Markov model to find that screening the adult population for CD using IgA EMA was cost-effective, compared with no screening. Hershcovici *et al.*[202] used a Markov model to find that mass screening via serological test followed by biopsy was cost-effective, compared with no screening. Park *et al.*[203] used a Markov model to find that universal serological screening (i.e. a pre-test probability close to the CD prevalence of 1%) to prevent non-traumatic hip and vertebral fractures was not cost-effective. However, this model did not consider the impact of osteoporosis patients without fracture, NHL or symptomatic relief via gluten-free diet, so it is likely to have underestimated cost-effectiveness. In the Dutch setting, Mohseninejad *et al.*[194] used a Markov model to find that screening patients with IBS symptoms for CD was cost-effective. Our model was largely based on the 2015 UK NICE model.[193] Our analysis extends its evaluation of active case-finding strategies. The earlier NICE evaluation found that screening first-degree relatives of people with CD was cost-effective among adults and children, that screening people with type 1 diabetes was cost-effective among adults and potentially cost-effective among children, and that screening those with autoimmune thyroid disease was not cost-effective among adults or children.

Chapter 10 Conclusions

Implications for practice

Our cost-effectiveness analysis suggested that, if serological testing is used alone, the most cost-effective strategy for adults is likely to be population-based screening (i.e. testing all adults with at least a 1% pre-test probability) with either IgA tTG or IgA EMA, or with a combination of both tests. Given the wider availability of IgA tTG in UK laboratories, the more objective interpretation of the test and its potential value in showing response to a gluten-free diet, we would recommend IgA tTG as the serological test to be used.[247] However, there is uncertainty in these results, and there is value, particularly for adult women, in conducting further research, such as through a long-term randomised controlled trial of screening strategies. Furthermore, decisions to implement population-based screening cannot be made based on this economic analysis alone: the proposed screening programme must meet UK National Screening Committee Criteria.[284] Although a CD screening programme meets some of these criteria, it does not yet meet all criteria (see *Appendix 29*). Key criteria that would need to be met before such a programme could be implemented are consensus on an appropriate threshold for the screening test (IgA tTG), agreement on further diagnostic workup for those testing positive for IgA tTG and randomised trials showing the effectiveness of the screening programme.

The cost-effectiveness analysis found that serological testing combined with HLA testing strategies with 1–20% pre-test probability had very similar cost-effectiveness to each other and to IgA tTG with a 1% pre-test probability. Given that population screening is not considered appropriate without additional evidence, the advantages of IgA tTG testing over IgA EMA testing and the difficulty of identifying patients with 5–20% pre-test probability, we recommend a strategy that combines HLA testing with IgA tTG testing in those with at least a 1.5% pre-test probability in adults. The cost-effectiveness analysis suggested that it was more cost-effective to perform the HLA test prior to the IgA tTG test. For children, the most cost-effective testing strategy is testing those with a 10% pre-test probability of having CD (more cost-effective than population screening). Indicators that should prompt testing are therefore those that increase the risk of CD to at least 1.5% in adults and to 10% in children. These are summarised in *Table 24*. These are diagnostic indicators identified by our review of diagnostic indicators (see *Chapter 3*) and through the prediction model (see *Chapter 4*).

However, recommending a strategy that involves testing a large proportion of people for the presence of the HLA genes may have unintended costs and consequences not captured by the economic model. As this test has low specificity, a large proportion of those who test positive would receive false-positive results: they would not have CD. All of these would require follow-up calls from a GP to discuss their test results and would have to be told that they have a genetic risk factor that puts them at risk of CD and other autoimmune conditions such as type 1 diabetes and rheumatoid arthritis. This could cause unnecessary patient concern.

All strategies evaluated assumed that biopsy confirmation would be used if the post-test probability following positive test results remained < 90%. Whether or not this is the case will depend on the pre-test probability of disease, and so it may be difficult to implement such a strategy in practice. The variation among individuals in their preferred diagnostic certainty and attitudes towards having a biopsy or following a gluten-free diet suggests that shared decision-making in which patient preferences are taken into account is important in determining the 'optimum' diagnostic pathway.

TABLE 24 Indicators that should prompt testing among men, women and children

Population	Indicator
All (men, women and children)	• First-degree relatives with CD • Anaemia • Iron, vitamin B_{12} or folate deficiency • Type 1 diabetes • Weight loss • Down syndrome • Thyroid disorders • GI symptoms • Fatigue • Migraine[a]
Adults only	• Osteoporosis • Mouth ulcers • IBS • Chronic liver disease • Epilepsy[a] • Cardiovascular disease[a] • Psoriasis[a]
Children only	• Delayed puberty[a]
Women and children	• IgA deficiency[a] • Turner syndrome
Women only	• Inflammatory bowel disease[a] • Systemic lupus erythematosus[a] • Fractures[a] • Neuropathy or ataxia

a Indicators not currently recommended in the NICE guidelines.[9]

Suggested research priorities

Given that the most cost-effective strategy based on the cost-effectiveness analysis was population-based screening, future work should consider whether or not population-based screening for CD could meet the UK National Screening Committee Criteria.[284] Key criteria that need further evaluation are the appropriate threshold for the screening test (IgA tTG), agreement on further diagnostic workup for those testing positive for IgA tTG and randomised trials showing the effectiveness of the screening programme. If the alternative strategy of IgA EMA plus HLA is recommended instead of population screening, then further research to measure the clinical effectiveness of these strategies is needed, in particular to consider the trade-off between improved sensitivity with using HLA first but with greater numbers of false-positive results.

The value-of-information analysis suggested that future research should focus on the probability of late (i.e. routine) diagnosis of CD and the accuracy of serological tests included in the model (IgA EMA and IgA tTG). The analysis also suggests that adult women should be the priority for research over adult men or children.

From a clinical perspective, further work to confirm thresholds above and below which we can confidently rule in or rule out CD would be of value, especially if population-based screening is being considered. The practice of dichotomising continuous test results may be an oversimplification of a complex disease with a wide range of clinical presentations. Identification of highly accurate serological testing strategies may allow for progressively more biopsy-avoidant pathways in the future. A meta-analysis based on individual patient data could be used to identify thresholds above and below which the risk of CD is sufficiently high to be ruled in or sufficiently low to be ruled out. Further testing,

either additional serological testing, genetic testing or biopsy, could then be recommended for patients with results between those values. This could allow a more evidence-based non-biopsy strategy similar to the strategies recommended by ESPGHAN[10] and the British Society of Gastroenterology,[19] which suggest that, for a person with a tTG level of at least 10 times the upper limit of normal, and who also tests positive for EMA, CD be diagnosied without biopsy confirmation.

There are further tests in development for CD that will require evaluation, with research focused on rapid point-of-care tests and genetic tests such as the *HLA-DQ*-gluten tetramer test.[285]

There is a need for large prospective cohort studies in which all participants receive accurate tests for CD to reduce bias in estimates of the diagnostic ability of indicators and to develop a more robust clinical prediction model. Accurate testing strategies that do not rely on invasive tests such as a duodenal biopsy would make this more feasible. It is important that diagnostic prediction models use data in which all patients have been tested for CD to reduce bias as a result of underdiagnosis. Prognostic cohort studies are also essential to identify predictors for CD for patients who are currently not diagnosed, because routinely collected data sets are biased as they depend on current testing practices and are more likely to pick up predictors that are already used to prompt testing.

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Avon Longitudinal Study of Parents and Children

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Contributions of authors

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Data-sharing statement

The data that support the findings of this study are available in the appendices and supplementary material. The data sets from the CPRD and ALSPAC are not publicly available because of data-sharing restrictions, but can be requested from the CPRD and the ALSPAC authors. All data requests should be submitted to the corresponding author for consideration.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Search strategies for diagnostic indicator review

Embase

1. Celiac Disease/ (29,729)
2. c?eliac.ti,kw. (22,813)
3. c?eliac.af. and gastroenterology.ec. (22,352)
4. (celiac or coeliac).ab. /freq=3 (9328)
5. or/1-4 (39,462)
6. ((detect* or diagnos* or identif* or decision* or predict* or prognos* or risk or risks or stratif* or validat*) adj3 (model* or factor* or algorithm? or scor* or system or technique? or aid? or rule or rules or index or variable* or tool? or panel or criteri* or characteristic? or history or finding* or value* or assay or stratif* or biomarker?)).ti,ab,kw. (2,855,495)
7. ((detect* or diagnos* or identif* or decision* or predict* or prognos* or stratif* or validat*) adj3 (risk or risks or model* or factor* or algorithm? or scor* or system or technique? or aid? or rule or rules or index or variable* or tool? or panel or criteri* or characteristic? or history or finding* or value* or assay or stratif* or biomarker?)).ti,ab,kw. (2,225,766)
8. (clinic* adj3 (model* or algorithm? or scor* or risk or risks or rule or rules or predict* or index or tool? or panel or criteri* or decision* or stratif* or diagnos* or detect* or identif* or probabilit*)).ti,ab,kw. (632,961)
9. ((multivaria* or multicomponent?) adj3 (model* or algorithm? or scor* or rule or rules or index or tool? or panel or criteri*)).ti,ab,kw. (110,662)
10. clinical decision making/ or statistical model/ or algorithm/ (444,594)
11. or/6-10 (3,678,637)
12. 5 and 11 (6036)
13. *physical disease by body function/ or exp *abnormal blood pressure/ or exp *abnormal posture/ or *aerophagia/ or exp *appetite disorder/ or *asthenia/ or *asymptomatic disease/ or exp *autonomic dysfunction/ or exp *balance disorder/ or exp *blood clotting disorder/ or exp *body temperature disorder/ or exp *body weight disorder/ or exp *common cold symptom/ or exp *consciousness disorder/ or exp *constipation/ or exp *coughing/ or exp *cyanosis/ or exp *diarrhea/ or exp *disability/ or exp *"disorders of higher cerebral function"/ or exp *dysphagia/ or *eructation/ or exp *faintness/ or exp *fatigue/ or *functional disease/ or exp *growth disorder/ or exp *immunopathology/ or exp *incontinence/ or exp *infertility/ or *listlessness/ or *malaise/ or *meningism/ or exp *metabolic disorder/ or exp *micturition disorder/ or exp *motor dysfunction/ or exp *multiple organ failure/ or exp *"nausea and vomiting"/ or exp *nutritional disorder/ or exp *pain/ or *pallor/ or exp *pregnancy disorder/ or *qi deficiency/ or *qi stagnation/ or exp *reflex disorder/ or exp *respiratory function disorder/ or exp *salivation disorder/ or exp *sensory dysfunction/ or exp *sexual dysfunction/ or exp *shock/ or exp *sleep disorder/ or exp *speech disorder/ or *weakness/ or *yang deficiency/ or *yin deficiency/ (4,991,033)
14. *physical disease by anatomical structure/ or exp *abdominal disease/ or exp *abnormal body build/ or exp *breast disease/ or exp *cardiovascular disease/ or exp *connective tissue disease/ or exp *digestive system disease/ or exp *ear nose throat disease/ or exp *endocrine disease/ or exp *eye disease/ or exp *"head and neck disease"/ or exp *hematologic disease/ or exp *mouth disease/ or exp *mucosal disease/ or exp *musculoskeletal disease/ or exp *neurologic disease/ or exp *pelvic disease/ or exp *respiratory tract disease/ or exp *skin disease/ or exp *soft tissue disease/ or exp *thorax disease/ or exp *urogenital tract disease/ (11,959,905)
15. *"physical disease by composition of body fluids, excreta and secretions"/ or exp *abnormal feces composition/ or exp *abnormal substrate concentration in blood/ or exp *abnormal urine composition/ or *dehydration/ or *hypervolemia/ (344,197)

16. ((addison* adj3 (disease* or disorder* or syndrom*)) or alopecia or baldness or amenorrhea* or amenorrhoea* or oligomenorrhea* or oligomenorrhoea* or anxiety disorder* or anorexia or adrenal insufficienc* or adrenocortical insufficienc* or allerg* or anemi* or anaemi* or angina or aneurysm or ankylosing spondylitis or arthropath* or arthriti* or arthrosis or arthroses or asthma* or asthenia or ataxia or atrial fibrillation or atrophy or autoimmune disorder* or (autoimmune adj (disease* or disorder* or syndrom*)) or ataxia or avitaminosis or bonnevie ullrich or back pain or (biliary adj3 (disease* or disorder* or syndrom*)) or (bipolar adj3 disorder*) or blindness or blind loop syndrom* or (blood adj3 poisoning) or brain atroph* or ((bone or bones) adj3 (broken or disease* or disorder* or syndrom*)) or (bone* adj3 (mineral* or densit* or soft* or decay*)) or (brain adj3 (disease* or disorder* or syndrom*)) or (bronchi* adj3 (disease* or disorder* or syndrom*)) or (bowel* adj3 (disease* or disorder* or syndrom*)) or calcinosis or cancer* or carcinoma* or adenocarcinoma* or neoplasm* or neoplastic or metasta* or malignan* or tumour or tumours or tumor or tumors or (cardiac adj3 (arrest or arrhythmia* or disease* or disorder* or surg* or syndrom*)) or cardiomyopath* or ((cardiovascular or coronary) adj3 (disease* or disorder* or event* or syndrom*)) or cachexia or ((cecal or colon* or duoden*) adj3 (disease* or disorder* or syndrom*)) or cerebral palsy or (cerebro* adj3 (degenerat* or disease* or disorder* or event* or syndrom*)) or chronic obstructive disease* or cirrhosis or claudication or colic or copd or ((coordination or co-ordination) adj3 (impair* or lack)) or congenital abnormalit* or (congential adj3 (disease* or disorder* or syndrom*)) or ((connective or collagen* or skin) adj3 (disease* or disorder* or syndrom*)) or collagenous sprue or colitis or colotides or coxarthrosis or crohn* or cushing* or cyanosis or cystic fibrosis or cystitis or deaf* or deformit* or delayed puberty or dental or depressive disorder* or dysphoria or dysthymia or disabled or (physical adj3 (deform* or disab* or impair*)) or dermatitis or dermato* or dorsopath* or diabet* or down* syndrom* or duhring* or duehring* or duhrig* or duehrig* or dyscoordination or dys-coordination or dys-coordination or dys-co-ordination or dysentery or dyssynergia or dys-synergia or emaciat* or enteritis or enterocolitis* or enteropathy or dystonia or eczema or edema or oedema or elfin face sydrom* or encephalopath* or (endocrine adj3 (disease* or disorder* or syndrom*)) or enuresis or enteropath* or epilep* or (eye adj3 (disease* or disorder* or manifestation* or syndrom*)) or fatigue syndrome or chronic fatigue or failure to thrive or fibromyalgia or fibrosis or food hypersensitivity or fractures or gammaglobulinemia or gammaglobulinaemia or (gardner* adj3 (syndrom* or disease* or disorder*)) or gastritis or gastroenteritis or gout or (glomerul* adj3 (disease* or disorder* or syndrom*)) or (gonodal adj3 dysgen*) or (growth adj3 (disease* or disorder* or syndrom*)) or headache* or ((hemic or haemic or lymph*) adj3 (disease* or disorder* or syndrom*)) or hematuria or haematuria or hemophili* or haemophili* or ((hearing or visual or vision or sight) adj3 (aid* or impair* or loss)) or (heart adj3 (disease* or disorder* or syndrom* or manifestation* or myopath*)) or hemiplegi* or hepatitis or hemodialysis or haemodialysis or (heart adj3 (disease* or disorder* or failure or syndrom*)) or hiv or human immunodeficiency virus or acquired immunodeficieny syndrom* or heerfordt waldenstrom* or hidroa or hydroa or hippel lindau* or hypertensi* or hypotensi* or hyperthyroidism or hypothyroidism or hypocortisolism or hypocorticism or hypoadrenalism or hyperthyroidism or hypothyroidism or incoordination or inco-ordination or in-coordination or in-co-ordination or infertility or subfertility or sub-fertility or sterility or inflammatory disease* or inflammatory bowel disease* or incontinen* or intestinal atresi* or intussusception or irritable bowel or ischemi* or ischaemi* or fistula* or (joint adj3 (disease* or disorder* or syndrom*)) or (jejunal adj3 (disease* or disorder* or syndrom*)) or kyphosis or lav-htlv* or leukemia or leukaemia or ((liver or hepatic) adj3 (disease* or disorder* or failure or syndrom*)) or lordosis or (lung adj3 (disease* or disorder*)) or lupus or lymphoma or lymphogranuloma* or lymphadenopath* or lymphotrop* or machado joseph* or macular degeneration or malnutrition or (mental adj2 (disorder* or disease* or health or illness*)) or mania or manic or (menstr* adj3 (ceas* or disturb* or disease* or disorder* or stop* or syndrom*)) or migraine* or (mitochondrial adj3 (disease* or disorder* or syndrom*)) or movement disorder* or mucinosis or musculoskeletal or narp syndrom* or necrotizing or nephrotic* or neuromuscular or non-hodgkin* or nonhodgkin* or multiple sclerosis or myeloma or myocarditis or myocardiopath* or myopath* or (myocardi* adj3 (deteri* or disease* or disorder* or syndrom* or manifestation*)) or nephrotic syndrome* or ((neurodegenerat*

or neuro-degenerat) adj3 (disease* or disorder* or syndrom*)) or ((nutritional or metabolic) adj3 (disease* or disorder* or syndrom*)) or ((organ* or kidney or stem cell) adj3 (transplant* or recipient*)) or (nervous system adj3 (disease* or disorder* or syndrom*)) or (neurological adj3 (condition* or disease* or disorder* or syndrom*)) or neuropath* or neurosarcoido* or occlusion* or obesity or obese or orthopedic* or orthopaedic* or ((esophageal or oesophageal) adj3 (disease* or disorder* or syndrom*)) or ((oral or mouth) adj3 (disease* or disorder* or syndrom* or manifestation*)) or osteo* or otitis media or otorhinolaryngolog* or otosclerosis or (pancrea* adj3 (disease* or disorder* or syndrom*)) or papulosquamous or paraplegi* or parkinson* or (peripheral adj3 (arterial or vascular or disease* or disorder* or syndrom*)) or (peritoneal adj3 (disease* or disorder* or syndrom*)) or photodermato* or pick disease* or pneumo* or polio* or polyp* or polydipsia or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or porphyrias or (pregnancy adj3 complicat*) or premature aging or proteostasis or pseudophakia or psoriasis or parapsoriasis or prolapse or (pulmonary adj3 (disease* or disorder* or syndrom*)) or purpur* or (recurren* adj3 (abortion* or miscarr*)) or (rect* adj3 (disease* or disorder* or syndrom*)) or ((renal or kidney) adj3 (disease* or disorder* or failure or syndrom*)) or (respiratory adj3 (disease* or disorder* or syndrom*)) or reticulocytosis or retinopathy or rheumat* or ricket* or sarcoido* or sepsis or septic* or seizure* or sclerosis or scoliosis or sickle cell or ((sjogren* or sjoegren* or sicca*) adj3 (syndrom* or disease* or disorder*)) or ((skin or connective tissue) adj3 (disease* or disorder* or syndrom*)) or sleep disorder* or sleep apnea or sleep apnoea or insomnia* or dyssomnia* or hypersomnia* or spina bifida or muscular atropy or short stature* or short bowel syndrom* or (spin* adj3 (degenerat* or disease* or disorder* or syndrom*)) or (spleen* adj3 (disease* or disorder* or syndrom*)) or spondylo* or stenosis* or stoma* or (stomach adj3 (disease* or disorder* or syndrom*)) or stroke or strokes or cerebral infarct* or tetraplegi* or thyroiditis* or (thyroid* adj3 (disease* or disorder* or dysfunction* or syndrom*)) or ((tooth or teeth or enamel) adj3 (decay* or discolo* or disease* or disorder* or dysfunction* or syndrom*)) or tropical sprue or tuberculosis or (systemic adj3 (disorder* or disease* or syndrom*)) or thrombocyto* or tremor or tremors or (turner* adj3 (syndrom* or disease* or disorder*)) or ulcer* or (urogenital adj3 (disease* or disorder* or syndrom*)) or vasculopath* or (vascular adj3 (disease* or disorder* or occlu* or syndrom*)) or vestibular or ((virus or viral or bacteri* or parasit*) adj3 (infection* or disease*)) or (wasting adj3 (disorder* or disease* or syndrom*)) or (whipple adj3 (disorder* or disease* or syndrom*)) or (william* adj3 (syndrom* or disease* or disorder*)) or zoster*).ti,ab,kw. (14,232,139)

17. ((digestive system* or duoden* or gastr* or intestin* or nutrition* or malabsor* or metabolic*) adj3 (disease* or disorder* or syndrom* or manifestation*)).ti,ab,kw. (254,303)
18. (constipation or constipated or diarrhoea or diarrhea or (abdominal adj3 (disten* or pain or bloating or cramp or cramps)) or flatulence or meteorism or steatorrhoea or steatorrhea or ((acid base or calcium or cyanocobalamin* or electrolyte* or folate or folic acid or glucose or IgA or immunoglobulin A or iron or lactose or lipid* or phosph* or protein* or triglyceride* or vitamin* or mineral*) adj3 (disorder* or deficien* or imbalance* or insufficiency or intoleran*)) or fever* or febrile or malaise or fatigue or letharg* or exhaustion or vomiting or nausea or emesis or sickness or weight loss or wait gain or hot flashes or hot flushes or medically unexplained or unexplained symptoms or unexplained medical or (signs adj2 symptoms) or sleepiness or ((calciferol or cholecalciferol or colecalciferol or egocalciferol) adj3 (disorder* or deficien* or imbalance* or insufficiency or intoleran*)) or conditions linked or linked conditions).ti,ab,kw. (1,126,673)
19. (medical* morbid* or (medical* adj3 comorbid*) or (medical* adj3 co-morbid*) or multimorbid* or multi* morbid* or multi* comorbid* or multi* co-morbid* or multi* physical*).ti,ab,kw. (30,923)
20. first-degree relative/ (6249)
21. ((first adj5 (relative* or relation?)) and c?eliac).ti,ab,kw. (452)
22. or/13-21 (18,446,309)
23. (((case? adj2 find*) or detect* or diagnos* or predict* or incidence or prevalence or seroprevalence* or risk or risk factor? or risk indicator? or screen* or test*) adj3 c?eliac*).ti,ab,kw. (7675)
24. (c?eliac and ((detect* or diagnos* or predict* or incidence or prevalence or seroprevalence* or risk or risk factor? or screen* or test*) adj2 CD)).ab. (3440)

25. (((association? or associated or indicator? or indicated or predict*) adj3 (risk? or symptom* or disease? or disorder? or histor*)) and c?eliac).ti,ab,kw. (4503)
26. ((association between or relationship between) and c?eliac?).ti,ab,kw. (2279)
27. *celiac disease/di [Diagnosis] (5931)
28. celiac disease/ and (*diagnosis/ or *differential diagnosis/ or *seroprevalence/ or *screening/ or *screening test/ or *incidence/ or *prevalence/) (1064)
29. celiac disease/ and ("prediction and forecasting"/ or prediction/ or predictive validity/ or predictive value/) (755)
30. or/23-29 (16,111)
31. 5 and 22 and 30 (15,090)
32. (((double* or dual*) adj5 diagnos* adj5 c?eliac?) or (comorbid* adj5 c?eliac)).ti,ab,kw. (85)
33. (high risk adj5 c?eliac?).ti,ab,kw. (103)
34. (famil* histor* adj2 c?eliac).ti,ab,kw. (93)
35. (children adj of* adj5 c?eliac).ti,ab,kw. (30)
36. celiac disease test kit/ (11)
37. or/32-36 (315)
38. 12 or 31 or 37 (17,603)
39. limit 38 to embase status (11,243)
40. ((celiac* or coeliac*) adj2 (asymptomatic or atypical or adolesc* or adult* or cases or cohort* or child* or disease* or family or families or familial or genetic predispos* or genetic pre-dispos* or heredit* or infant* or men or patient* or people or population* or subjects or symptomatic or syndrom* or sprue or women)).ti,ab,kw. (26,735)
41. limit 40 to (article-in-press status or in-process status) (372)
42. c?eliac.ti. (20,558)
43. limit 38 to conference abstract status (4569)
44. 42 and 43 (2794)
45. 39 or 41 or 44 (14,409)
46. ((celiac* or coeliac*) adj (angiograp* or arter* or axis or plexus or trunk)).ti,ab,kw,hw. (12,186)
47. case report.ti. (283,693)
48. ((case adj of*) and (patient or man or woman)).ti,ab. and case report.sh. (347,041)
49. (editorial or letter).pt. (1,747,770)
50. (exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp marine species/ or nonhuman/ or animal.hw.) not human/ (6,072,159)
51. ((rat or rats or mouse or mice or rodent* or animal* or murine or porcine or feline or canine or dog or dogs or cat or cats or pig or pigs or monkey* or macaque*) not human*).ti. (1,957,387)
52. or/46-51 (8,620,748)
53. 45 not 52 (12,083)
54. case control study/ or hospital based case control study/ or population based case control study/ or exp longitudinal study/ or prospective study/ or retrospective study/ (1,667,885)
55. case finding/ or cohort analysis/ or control group/ or correlational study/ or cross-sectional study/ (1,006,525)
56. seroepidemiology/ (3934)
57. (cohort or case control* or case finding or cross-sectional or longitudinal).ti,ab,kw. (1,661,606)
58. study.ti. (1,569,542)
59. (study and (analys* or cases or clinical or control* or compar* or correlat* or associat* or epidemiolog* or evaluat* or examin* or investigat* or observ* or population based or prospectiv* or retrospectiv* or serolog*)).ti,ab,kw. (8,983,424)
60. (case? and control*).ab. (657,067)
61. (controls or (control adj (group? or participants or patients))).ab. (1,656,326)
62. (groups or subgroup? or sub-group?).ab. (3,028,674)
63. (group? adj5 (analys* or compar* or control* or correlat* or associat*)).ab. (1,489,755)

64. exp regression analysis/ (434,324)
65. statistical model/ (158,724)
66. ((analys* or logistic*) adj1 (model* or regression*)).ab. (661,228)
67. study.ab. /freq=2 (3,165,201)
68. or/54-67 (12,212,707)
69. 53 and 68 (7566)
70. limit 69 to yr="1997 –Current" (7032)

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Date range searched: 1946 to 5 February 2020.

1. Celiac Disease/ (19,693)
2. c?eliac.ti,ab,kf. (27,278)
3. or/1-2 (32,722)
4. ((detect* or diagnos* or identif* or decision* or predict* or prognos* or risk or risks or stratif* or validat*) adj3 (model* or factor* or algorithm? or scor* or system or technique? or aid? or rule or rules or index or variable* or tool? or panel or criteri* or characteristic? or history or finding* or value* or assay or stratif* or biomarker?)).ti,ab,kf. (1,978,188)
5. ((detect* or diagnos* or identif* or decision* or predict* or prognos* or stratif* or validat*) adj3 (risk or risks or model* or factor* or algorithm? or scor* or system or technique? or aid? or rule or rules or index or variable* or tool? or panel or criteri* or characteristic? or history or finding* or value* or assay or stratif* or biomarker?)).ti,ab,kf. (154,7617)
6. (clinic* adj3 (model* or algorithm? or scor* or risk or risks or rule or rules or predict* or index or tool? or panel or criteri* or decision* or stratif* or diagnos* or detect* or identif* or probabilit*)).ti,ab,kf. (420,165)
7. ((multivaria* or multicomponent?) adj3 (model* or algorithm? or scor* or rule or rules or index or tool? or panel or criteri*)).ti,ab,kf. (69,716)
8. (clinical decision making or (decision and logistic models)).sh. (7874)
9. or/4-8 (2,337,727)
10. 3 and 9 (3401)
11. Risk Factors/or Disease Predisposition/or Genetic Predisposition to Disease/(907,433)
12. exp "bacterial infections and mycoses"/or exp virus diseases/or exp parasitic diseases/or exp neoplasms/or exp musculoskeletal diseases/or exp stomatognathic diseases/or exp respiratory tract diseases/or exp otorhinolaryngologic diseases/or exp nervous system diseases/or exp eye diseases/or exp male urogenital diseases/or exp "female urogenital diseases and pregnancy complications"/or exp cardiovascular diseases/or exp "hemic and lymphatic diseases"/or exp "congenital, hereditary, and neonatal diseases and abnormalities"/or exp "skin and connective tissue diseases"/or exp endocrine system diseases/or exp immune system diseases/or exp "disorders of environmental origin"/or disease/or digestive system diseases/or exp biliary tract diseases/or exp digestive system abnormalities/or exp digestive system fistula/or exp digestive system neoplasms/or exp liver diseases/or exp pancreatic diseases/or exp peritoneal diseases/or gastrointestinal diseases/or exp esophageal diseases/or exp gastroenteritis/or exp gastrointestinal hemorrhage/or exp gastrointestinal neoplasms/or intestinal diseases/or exp cecal diseases/or exp colonic diseases/or exp duodenal diseases/or exp dysentery/or exp enteritis/or exp enterocolitis/or exp hiv enteropathy/or exp ileal diseases/or exp inflammatory bowel diseases/or exp intestinal atresia/or exp intestinal diseases, parasitic/or exp intestinal fistula/or exp intestinal neoplasms/or exp intestinal obstruction/or exp intestinal perforation/or exp intestinal polyposis/or exp jejunal diseases/or malabsorption syndromes/or blind loop syndrome/or collagenous sprue/or lactose intolerance/or short bowel syndrome/or sprue, tropical/or steatorrhea/or whipple disease/or mesenteric ischemia/or mesenteric vascular occlusion/or pneumatosis cystoides intestinalis/or protein-losing enteropathies/or exp rectal diseases/or zollinger-ellison syndrome/or exp stomach

diseases/or exp tuberculosis, gastrointestinal/or exp visceral prolapse/or exp liver diseases/or exp pancreatic diseases/or exp peritoneal diseases/or "nutritional and metabolic diseases"/or metabolic diseases/or exp acid-base imbalance/or exp bone diseases, metabolic/or exp brain diseases, metabolic/ or exp calcium metabolism disorders/or exp dna repair-deficiency disorders/or exp glucose metabolism disorders/or exp hyperlactatemia/or exp iron metabolism disorders/or exp lipid metabolism disorders/or malabsorption syndromes/or exp blind loop syndrome/or exp collagenous sprue/or exp hyperhomocysteinemia/or exp lactose intolerance/or exp sprue, tropical/or exp steatorrhea/or exp whipple disease/or exp metabolic syndrome/or exp metabolism, inborn errors/or exp mitochondrial diseases/or exp phosphorus metabolism disorders/or exp porphyrias/or exp proteostasis deficiencies/or exp skin diseases, metabolic/or exp wasting syndrome/or exp water-electrolyte imbalance/or exp nutrition disorders/or "SIGNS and SYMPTOMS"/or exp aging, premature/or exp asthenia/or exp body temperature changes/or exp body weight/or exp cardiac output, high/or exp cardiac output, low/or exp chills/or exp cyanosis/or exp edema/or exp eye manifestations/or exp failure to thrive/or exp fatigue/or exp feminization/or exp fetal distress/or exp heart murmurs/or exp hot flashes/or exp hypergammaglobulinemia/or exp hyperlactatemia/or exp hypertriglyceridemic waist/or exp intermittent claudication/or exp medically unexplained symptoms/or exp mobility limitation/or exp motion sickness/or exp myocardial stunning/or exp neurologic manifestations/or exp oral manifestations/or exp polydipsia/or exp prodromal symptoms/or exp pseudophakia/or exp renal colic/or exp reticulocytosis/ or exp "signs and symptoms, digestive"/or exp "signs and symptoms, respiratory"/or exp skin manifestations/or exp sleepiness/or exp travel-related illness/or exp urological manifestations/ or exp virilism/ (13,521,118)

13. exp "anatomy (non mesh)"/ab, pa [abnormalities, pathology] (1,686,610)
14. ((addison* adj3 (disease* or disorder* or syndrom*)) or alopecia or baldness or amenorrhea* or amenorrhoea* or oligomenorrhea* or oligomenorrhoea* or anxiety disorder* or anorexia or adrenal insufficienc* or adrenocortical insufficienc* or allerg* or anemi* or anaemi* or angina or aneurysm or ankylosing spondylitis or arthropath* or arthriti* or arthrosis or arthroses or asthma* or asthenia or ataxia or atrial fibrillation or atrophy or autoimmune disorder* or (autoimmune adj (disease* or disorder* or syndrom*)) or ataxia or avitaminosis or bonnevie ullrich or back pain or (biliary adj3 (disease* or disorder* or syndrom*)) or (bipolar adj3 disorder*) or blindness or blind loop syndrom* or (blood adj3 poisoning) or brain atroph* or ((bone or bones) adj3 (broken or disease* or disorder* or syndrom*)) or (bone* adj3 (mineral* or densit* or soft* or decay*)) or (brain adj3 (disease* or disorder* or syndrom*)) or (bronchi* adj3 (disease* or disorder* or syndrom*)) or (bowel* adj3 (disease* or disorder* or syndrom*)) or calcinosis or cancer* or carcinoma* or adenocarcinoma* or neoplasm* or neoplastic or metasta* or malignan* or tumour or tumours or tumor or tumors or (cardiac adj3 (arrest or arrhythmia* or disease* or disorder* or surg* or syndrom*)) or cardiomyopath* or ((cardiovascular or coronary) adj3 (disease* or disorder* or event* or syndrom*)) or cachexia or ((cecal or colon* or duoden*) adj3 (disease* or disorder* or syndrom*)) or cerebral palsy or (cerebro* adj3 (degenerat* or disease* or disorder* or event* or syndrom*)) or chronic obstructive disease* or cirrhosis or claudication or colic or copd or ((coordination or co-ordination) adj3 (impair* or lack)) or congenital abnormalit* or (congential adj3 (disease* or disorder* or syndrom*)) or ((connective or collagen* or skin) adj3 (disease* or disorder* or syndrom*)) or collagenous sprue or colitis or colotides or coxarthrosis or crohn* or cushing* or cyanosis or cystic fibrosis or cystitis or deaf* or deformit* or delayed puberty or dental or depressive disorder* or dysphoria or dysthymia or disabled or (physical adj3 (deform* or disab* or impair*)) or dermatitis or dermato* or dorsopath* or diabet* or down* syndrom* or duhring* or duehring* or duhrig* or duehrig* or dyscoordination or dys-coordination or dys-coordination or dys-co-ordination or dysentery or dyssynergia or dys-synergia or emaciat* or enteritis or enterocolitis* or enteropathy or dystonia or eczema or edema or oedema or elfin face sydrom* or encephalopath* or (endocrine adj3 (disease* or disorder* or syndrom*)) or enuresis or enteropath* or epilep* or (eye adj3 (disease* or disorder* or manifestation* or syndrom*)) or fatigue syndrome or chronic fatigue or failure to thrive or fibromyalgia or fibrosis or food hypersensitivity or fractures or gammaglobulinemia or gammaglobulinaemia or (gardner* adj3 (syndrom* or disease* or disorder*)) or gastritis or gastroenteritis or gout or (glomerul* adj3 (disease* or disorder* or syndrom*)) or (gonodal adj3 dysgen*) or (growth adj3 (disease* or disorder* or syndrom*)) or headache* or

((hemic or haemic or lymph*) adj3 (disease* or disorder* or syndrom*)) or hematuria or haematuria or hemophili* or haemophili* or ((hearing or visual or vision or sight) adj3 (aid* or impair* or loss)) or (heart adj3 (disease* or disorder* or syndrom* or manifestation* or myopath*)) or hemiplegi* or hepatitis or hemodialysis or haemodialysis or (heart adj3 (disease* or disorder* or failure or syndrom*)) or hiv or human immunodeficiency virus or acquired immunodeficieny syndrom* or heerfordt waldenstrom* or hidroa or hydroa or hippel lindau* or hypertensi* or hypotensi* or hyperthyroidism or hypothyroidism or hypocortisolism or hypocorticism or hypoadrenalism or hyperthyroidism or hypothyroidism or incoordination or inco-ordination or in-coordination or in-co-ordination or infertility or subfertility or sub-fertility or sterility or inflammatory disease* or inflammatory bowel disease* or incontinen* or intestinal atresi* or intussusception or irritable bowel or ischemi* or ischaemi* or fistula* or (joint adj3 (disease* or disorder* or syndrom*)) or (jejunal adj3 (disease* or disorder* or syndrom*)) or kyphosis or lav-htlv* or leukemia or leukaemia or ((liver or hepatic) adj3 (disease* or disorder* or failure or syndrom*)) or lordosis or (lung adj3 (disease* or disorder*)) or lupus or lymphoma or lymphogranuloma* or lymphadenopath* or lymphotrop* or machado joseph* or macular degeneration or malnutrition or (mental adj2 (disorder* or disease* or health or illness*)) or mania or manic or (menstr* adj3 (ceas* or disturb* or disease* or disorder* or stop* or syndrom*)) or migraine* or (mitochondrial adj3 (disease* or disorder* or syndrom*)) or movement disorder* or mucinosis or musculoskeletal or narp syndrom* or necrotizing or nephrotic* or neuromuscular or non-hodgkin* or nonhodgkin* or multiple sclerosis or myeloma or myocarditis or myocardiopath* or myopath* or (myocardi* adj3 (deteri* or disease* or disorder* or syndrom* or manifestation*)) or nephrotic syndrome* or ((neurodegenerat* or neuro-degenerat) adj3 (disease* or disorder* or syndrom*)) or ((nutritional or metabolic) adj3 (disease* or disorder* or syndrom*)) or ((organ* or kidney or stem cell) adj3 (transplant* or recipient*)) or (nervous system adj3 (disease* or disorder* or syndrom*)) or (neurological adj3 (condition* or disease* or disorder* or syndrom*)) or neuropath* or neurosarcoido* or occlusion* or obesity or obese or orthopedic* or orthopaedic* or ((esophageal or oesophageal) adj3 (disease* or disorder* or syndrom*)) or ((oral or mouth) adj3 (disease* or disorder* or syndrom* or manifestation*)) or osteo* or otitis media or otorhinolaryngolog* or otosclerosis or (pancrea* adj3 (disease* or disorder* or syndrom*)) or papulosquamous or paraplegi* or parkinson* or (peripheral adj3 (arterial or vascular or disease* or disorder* or syndrom*)) or (peritoneal adj3 (disease* or disorder* or syndrom*)) or photodermato* or pick disease* or pneumo* or polio* or polyp* or polydipsia or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or porphyrias or (pregnancy adj3 complicat*) or premature aging or proteostasis or pseudophakia or psoriasis or parapsoriasis or prolapse or (pulmonary adj3 (disease* or disorder* or syndrom*)) or purpur* or (recurren* adj3 (abortion* or miscarr*)) or (rect* adj3 (disease* or disorder* or syndrom*)) or ((renal or kidney) adj3 (disease* or disorder* or failure or syndrom*)) or (respiratory adj3 (disease* or disorder* or syndrom*)) or reticulocytosis or retinopathy or rheumat* or ricket* or sarcoido* or sepsis or septic* or seizure* or sclerosis or scoliosis or sickle cell or ((sjogren* or sjoegren* or sicca*) adj3 (syndrom* or disease* or disorder*)) or ((skin or connective tissue) adj3 (disease* or disorder* or syndrom*)) or sleep disorder* or sleep apnea or sleep apnoea or insomnia* or dyssomnia* or hypersomnia* or spina bifida or muscular atropy or short stature* or short bowel syndrom* or (spin* adj3 (degenerat* or disease* or disorder* or syndrom*)) or (spleen* adj3 (disease* or disorder* or syndrom*)) or spondylo* or stenosis* or stoma* or (stomach adj3 (disease* or disorder* or syndrom*)) or stroke or strokes or cerebral infarct* or tetraplegi* or thyroiditis* or (thyroid* adj3 (disease* or disorder* or dysfunction* or syndrom*)) or ((tooth or teeth or enamel) adj3 (decay* or discolo* or disease* or disorder* or dysfunction* or syndrom*)) or tropical sprue or tuberculosis or (systemic adj3 (disorder* or disease* or syndrom*)) or thrombocyto* or tremor or tremors or (turner* adj3 (syndrom* or disease* or disorder*)) or ulcer* or (urogenital adj3 (disease* or disorder* or syndrom*)) or vasculopath* or (vascular adj3 (disease* or disorder* or occlu* or syndrom*)) or vestibular or ((virus or viral or bacteri* or parasit*) adj3 (infection* or disease*)) or (wasting adj3 (disorder* or disease* or syndrom*)) or (whipple adj3 (disorder* or disease* or syndrom*)) or (william* adj3 (syndrom* or disease* or disorder*)) or zoster*).ti,ab,kf. (11,316,008)

15. ((digestive system* or duoden* or gastr* or intestin* or nutrition* or malabsor* or metabolic*) adj3 (disease* or disorder* or syndrom* or manifestation*)).ti,ab,kf. (180,683)

16. (constipation or constipated or diarrhoea or diarrhea or (abdominal adj3 (disten* or pain or bloating or cramp or cramps)) or flatulence or meteorism or steatorrhoea or steatorrhea or ((acid base or calcium or cyanocobalamin* or electrolyte* or folate or folic acid or glucose or IgA or immunoglobulin A or iron or lactose or lipid* or phosph* or protein* or triglyceride* or vitamin* or mineral*) adj3 (disorder* or deficien* or imbalance* or insufficiency or intoleran*)) or fever* or febrile or malaise or fatigue or letharg* or exhaustion or vomiting or nausea or emesis or sickness or weight loss or wait gain or hot flashes or hot flushes or medically unexplained or unexplained symptoms or unexplained medical or (signs adj2 symptoms) or sleepiness or ((calciferol or cholecalciferol or colecalciferol or egocalciferol) adj3 (disorder* or deficien* or imbalance* or insufficiency or intoleran*)) or conditions linked or linked conditions).ti,ab,kf. (805,001)
17. (medical* morbid* or (medical* adj3 comorbid*) or (medical* adj3 co-morbid*) or multimorbid* or multi* morbid* or multi* comorbid* or multi* co-morbid* or multi* physical*).ti,ab,kf. (18,919)
18. (first-degree relative or family or family relation or family history or mother or father or parent or daughter or son).sh. or (brother or sister or sibling).hw. (83,159)
19. (first adj5 (relative* or relation?)).ti,ab,kf. (21,485)
20. (children adj of*).ti,ab,kf. (32,315)
21. or/11-20 (16,944,516)
22. (((case? adj2 find*) or detect* or diagnos* or predict* or incidence or prevalence or seroprevalence* or risk or risk factor? or risk indicator? or screen* or test*) adj3 c?eliac*).ti,ab,kf. (4839)
23. (c?eliac and ((detect* or diagnos* or predict* or incidence or prevalence or seroprevalence* or risk or risk factor? or screen* or test*) adj2 CD)).ab. (1782)
24. (((association? or associated or indicator? or indicated or predict*) adj3 (risk? or symptom* or disease? or disorder? or histor*)) and c?eliac).ti,ab,kf. (2819)
25. ((association between or relationship between) and c?eliac?).ti,ab,kf. (1328)
26. celiac disease/di [Diagnosis] (5652)
27. celiac disease/and (diagnosis/or diagnosis, differential/or seroprevalence/or seroepidemiologic studies/or screening/or prediction/or prevalence/or incidence/) (2995)
28. or/22-27 (11,534)
29. 3 and 21 and 28 (9724)
30. Celiac Disease/di and (atypical or extraintestinal or extra-intestinal or nonspecific or non-specific).mp. (490)
31. (((double* or dual*) adj5 diagnos* adj5 c?eliac?) or (comorbid* adj5 c?eliac)).ti,ab,kf. (42)
32. (high risk adj5 c?eliac?).ti,ab,kf. (67)
33. (famil* histor* adj2 c?eliac).ti,ab,kf. (33)
34. (children adj of* adj5 c?eliac).ti,ab,kw. (19)
35. or/30-34 (642)
36. 10 or 29 or 35 (11,362)
37. ((celiac* or coeliac*) adj2 (asymptomatic or atypical or adolesc* or adult* or cases or cohort* or child* or disease* or family or families or familial or genetic predispos* or genetic pre-dispos* or heredit* or infant* or men or patient* or people or population* or subjects or symptomatic or syndrom* or sprue or women)).ti,ab,kf. (18,800)
38. limit 37 to ("in data review" or in process or publisher) (605)
39. 36 or 38 (11,704)
40. ((celiac* or coeliac*) adj (angiograp* or arter* or axis or plexus or trunk)).ti,ab,kf,hw. (8461)
41. case report.ti. (230,986)
42. ((case adj of*) and (patient or man or woman)).ti,ab. and case reports.pt. (252,275)
43. (comment or editorial or letter or newspaper article).pt. (1,825,467)
44. (exp Animals/or exp Animal Experimentation/or exp Models, Animal/or exp Animals, Laboratory/or exp rodentia/) not Humans/ (4,673,001)
45. ((rat or rats or mouse or mice or rodent* or animal* or murine or porcine or feline or canine or dog or dogs or cat or cats or pig or pigs or monkey* or macaque*) not human*).ti. (1,856,683)
46. or/40-45 (7,137,365)
47. 39 not 46 (9645)

48. exp epidemiologic studies/ (2,435,409)
49. (cohort or case control* or case finding or cross-sectional or longitudinal).ti,ab,kf. (1,114,977)
50. study.ti. (1,330,964)
51. (study and (analys* or cases or clinical or control* or compar* or correlat* or associat* or epidemiolog* or evaluat* or examin* or investigat* or observ* or population based or prospectiv* or retrospectiv* or serolog*)).ti,ab,kf. (6,665,955)
52. (case? and control*).ab. (448,997)
53. (controls or (control adj (group? or participants or patients))).ab. (1,189,049)
54. (groups or subgroup? or sub-group?).ab. (2,170,205)
55. (group? adj5 (analys* or compar* or control* or correlat* or associat*)).ab. (1,004,351)
56. exp Regression Analysis/ (416,341)
57. statistical model/ (89,771)
58. ((analys* or logistic*) adj1 (model* or regression*)).ab. (456,097)
59. study.ab./freq=2 (2,157,950)
60. or/48-59 (9,618,005)
61. 47 and 60 (5419)
62. limit 61 to yr="1997 -Current" (4786)

Cochrane Library, Issue 2 of 12, 2020

#1 MeSH descriptor: [Celiac Disease] this term only (63)
#2 ("celiac disease" or "coeliac disease"): kw (338)
#3 ((celiac* or coeliac*) near/3 (asymptomatic or atypical or adolesc* or adult* or cases or cohort* or child* or disease* or family or families or familial or genetic predispos* or genetic pre-dispos* or heredit* or infant* or men or patient* or people or population* or subjects or symptomatic or syndrom* or sprue or women)):ti,ab (782)
#4 (#1 or #2 or #3) (886)
#5 ((celiac* or coeliac*) next (angiograp* or arter* or axis or plexus or trunk)):ti,ab,kw (276)
#6 #4 not #5 (*n* = 870) (870)

Web of Science: Science Citation Index Expanded® (Clarivate) (SCI-EXPANDED), Conference Proceedings Citation Index – Social Sciences Citation Index™ (Clarivate) (SSCI)

(Limit to celiac or coeliac in title/abstract, *n* = 6118.)

#28 (#26 not #27) (7430)
#27 (TI=("case report" or "a case of" or "a rare case of")) or (TS=(("a case of" or "a rare case of") near (patient or man or woman or child or adolescent or "an adult"))) (202,526)
#26 (#25 AND #24) [7493]
Indexes=SCI-EXPANDED, CPCI-S Timespan=1997-2020
#25 ((TS=(seroepidemiolog* or cohort or "case control*" or "case find*" or cross-sectional or longitudinal or "population based" or prospective* or retrospective*) or TI=(study) or TS=(study and (analys* or cases or clinical or control* or compar* or correlat* or associat* or epidemiolog* or evaluat* or examin* or investigat* or observ* or population based or prospectiv* or retrospectiv* or serolog*)) or TS=((case or cases) and control*) or TS=(controls or "control* group*" or "control* participant*" or "control* patient*" or groups or subgroup* or sub-group*) or TS=(group* near (analys* or compar* or control* or correlat* or associat*)) or TS=("regression analysis" or "regression model*" or "statistical model*" or "logistic* model*")) NOT (TI=(rat or rats or mouse or mice or rodent* or animal* or murine or porcine or feline or canine or dog or dogs or cat or cats or pig or pigs or monkey* or macaque* or nonhuman or "non human"))) (19,956,721)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

#24 (#23 OR #22 OR #21 OR #8) (13,272)
#23 (TS=((“high risk” or “famil* histor*” or “child* of”) near (celiac or coeliac)) or TS=(“celiac disease test kit”)) (233)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#22 (TS=((double* or dual*) near diagnos* near (celiac or coeliac))) or (TS=(comorbid* near (celiac or coeliac))) (111)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#21 (#20 AND #15 AND #1) (12,140)
#20 (#19 OR #18 OR #17 OR #16) (18,586)
#19 (TS=((“association* between” or “relationship between”) and (celiac or coeliac))) (1458)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#18 ((TS=((association* or associated or indicator* or indicated or predict*) near (risk* or symptom* or disease* or disorder* or histor*))) and (TS=(celiac or coeliac))) (5833)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#17 (TS=((celiac or coeliac) and (“detect* CD” or “CD detect*” or “detect* of CD” or “detect* with CD” or “diagnos* CD” or “CD diagnos*” or “diagnos* of CD” or “diagnos* with CD” or “predict* CD” or “CD predict*” or “predict* of CD” or “predict* with CD” or “inciden* CD” or “CD inciden*” or “inciden* of CD” or “inciden* with CD” or “prevalen* CD” or “CD prevalen*” or “prevalen* of CD” or “ prevalen* with CD” or “seroprevalen* CD” or “CD seroprevalen*” or “seroprevalen* of CD” or “seroprevalen* with CD” or “CD risk*” or “risk* of CD” or “risk* for CD” or “risk* factor* of CD” or “risk factor* for CD” or “CD screen*” or “screen* for CD” or “CD test*” or “test* for CD”))) (1489)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#16 (TS=((“case finding” or detect* or diagnos* or predict* or incidence or prevalence or seroprevalence* or risk or “risk factor*” or “risk indicator*” or screen* or test*) and (celiac* or coeliac*))) (17,056)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#15 (#14 OR #13 OR #12 OR #11 OR #10 OR #9) (14,174,134)
#14 (TI=(manifestation*)) (51,353)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#13 (TS=(“first degree” near (related or relative* or relation*))) (11,114)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#12 (TS=(“medical* morbid*” or (medical* near (comorbid* or co-morbid*)) or multimorbid* or “multi* morbid*” or “multi* comorbid*” or “multi* co-morbid*” or “multi* physical*”)) (25,013)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#11 ((TS=(constipation or constipated or diarrhoea or diarrhea or (abdominal near (disten* or pain or bloating or cramp or cramps)) or flatulence or meteorism or steatorrhoea or steatorrhea)) or (TS=((“acid base” or calcium or cyanocobalamin* or electrolyte* or folate or “folic acid”or glucose or IgA or “immunoglobulin A” or iron or lactose or lipid* or phosph* or protein* or triglyceride* or vitamin* or mineral*) near (disorder* or deficien* or imbalance* or insufficiency or intoleran*))) or (TS=(fever* or febrile or malaise or fatigue or letharg* or exhaustion or vomiting or nausea or emesis or sickness or “weight loss” or “wait gain” or “hot flashes” or “hot flushes” or “medically unexplained” or “unexplained medical” or “unexplained symptom*” or “signs and symptoms” or “condition* linked” or “linked condition*” or “condition* associated with” or sleepiness)) or (TS=((calciferol or cholecalciferol or colecalciferol or egocalciferol) near (disorder* or deficien* or imbalance* or insufficiency or intoleran*)))) or (TS=((anxiety or depression or mood) near (celiac or coeliac))) (1,055,350)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#10 (TS=(“digestive system* disease*” or “digestive system* disorder*” or “digestive system* syndrom*” or “digestive system manifestation*” or “duoden* disease*” or “duoden* disorder*” or “duoden* syndrom*” or “duoden* manifestation*” or “gastr* disease*” or “gastr* disorder*” or “gastr* syndrom*” or “gastr* manifestation*” or “intestin* disease*” or “intestin* disorder*” or “intestin* syndrom*” or “intestin* manifestation*” or “malabsor* disease*” or “malabsor* disorder*” or “malabsor* syndrom*” or “malabsor* manifestation*”)) (29,189)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

#9 (TS=((addison* near (disease* or disorder* or syndrom*)) or alopecia or baldness or amenorrhea* or amenorrhoea* or oligomenorrhea* or oligomenorrhoea* or "anxiety disorder*" or anorexia or "adrenal insufficienc*" or "adrenocortical insufficienc*" or allerg* or anemi* or anaemi* or angina or aneurysm or "ankylosing spondylitis" or arthropath* or arthriti* or arthrosis or arthroses or asthma* or asthenia or ataxia or "atrial fibrillation" or atrophy or "autoimmune disorders" or "autoimmune diseases" or "autoimmune syndrom*" or ataxia or avitaminosis or "bonnevie ullrich" or "back pain" or (biliary near (disease* or disorder* or syndrom*)) or (bipolar near disorder*) or blindness or "blind loop syndrom*" or (blood near poisoning) or "brain atroph*" or ((bone or bones) near (broken or disease* or disorder* or syndrom*)) or (bone* near (mineral* or densit* or soft* or decay*)) or (brain near (disease* or disorder* or syndrom*)) or (bronchi* near (disease* or disorder* or syndrom*)) or (bowel* near (disease* or disorder* or syndrom*)) or calcinosis or cancer* or carcinoma* or adenocarcinoma* or neoplasm* or neoplastic or metasta* or malignan* or tumour or tumours or tumor or tumors or (cardiac near (arrest or arrhythmia* or disease* or disorder* or surg* or syndrom*)) or cardiomyopath* or ((cardiovascular or coronary) near (disease* or disorder* or event* or syndrom*)) or cachexia or ((cecal or colon* or duoden*) near (disease* or disorder* or syndrom*)) or "cerebral palsy" or (cerebro* near (degenerat* or disease* or disorder* or event* or syndrom*)) or "chronic obstructive disease" or cirrhosis or claudication or colic or COPD or ((coordination or co-ordination) near (impair* or lack)) or "congenital abnormalit*" or (congential near (disease or disorder* or syndrom*)) or ((connective or collagen* or skin) near (disease or disorder* or syndrom*)) or "collagenous sprue" or colitis or colotides or coxarthrosis or crohn* or cushing* or cyanosis or "cystic fibrosis" or cystitis or deaf* or deformit* or "delayed puberty" or dental or "depressive disorder*" or dysphoria or dysthymia or disabled or (physical near (deform* or disab* or impair*)) or dermatitis or dermato* or dorsopath* or diabet* or "down* syndrom*" or duhring* or duehring* or duhrig* or duehrig* or dyscoordination or dys-coordination or dys-coordination or dys-co-ordination or dysentery or dyssynergia or dys-synergia or emaciat* or enteritis or enterocolitis* or dystonia or eczema or edema or oedema or "elfin face sydrom*" or encephalopath* or (endocrine near (disease* or disorder* or syndrom*)) or enuresis or enteropath* or epilep* or (eye near (disease* or disorder* or manifestation* or syndrome*)) or "fatigue syndrome" or "chronic fatigue" or "failure to thrive" or fibromyalgia or fibrosis or "food hypersensitivity" or fractures or gammaglobulinemia or gammaglobulinaemia or (gardner* near (syndrom* or disease* or disorder*)) or gastritis or gastroenteritis or gout or (glomerul* near (disease* or disorder* or syndrom*)) or "gonodal near dysgen*" or (growth near (disease* or disorder* or syndrom*)) or headache* or ((hemic or haemic or lymph*) near (disease* or disorder* or syndrom*)) or hematuria or haematuria or hemophili* or haemophili* or ((hearing or visual or vision or sight) near (aid* or impair* or loss)) or (heart near (disease* or disorder* or failure or syndrom* or manifestation* or myopathy*)) or hemiplegi* or hepatitis or hemodialysis or haemodialysis hiv or "human immunodeficiency virus" or "acquired immunodeficieny syndrom*" or "heerfordt waldenstrom*" or hidroa or hydroa or "hippel lindau*" or hypertensi* or hypotensi* or hyperthyroidism or hypothyroidism or hypocortisolism or hypocorticism or hypoadrenalism or incoordination or inco-ordination or in-coordination or in-co-ordination or infertility or subfertility or sub-fertil* or sterility or "inflammatory disease*" or "inflammatory bowel disease*" or incontinen* or "intestinal atresi*" or intussusception or "irritable bowel" or ischemi* or ischaemi* or fistula* or (joint near (disease* or disorder* or syndrom*)) or (jejunal near (disease* or disorder* or syndrom*)) or kyphosis or lav-htlv* or leukemia or leukaemia or ((liver or hepatic) near (disease* or disorder* or failure or syndrom*)) or lordosis or (lung near (disease* or disorder*)) or lupus or SLE or lymphoma or lymphogranuloma* or lymphadenopath* or lymphotrop* or "machado joseph*" or "macular degeneration" or malnutrition or (mental near (disorder* or disease* or health or illness*)) or mania or manic or (menstr* near (ceas* or disturb* or disease* or disorder* or stop* or syndrom*)) or migraine* or (mitochondrial near (disease* or disorder* or syndrom*)) or "movement disorder*" or mucinosis or musculoskeletal or "narp syndrom*" or necrotizing or nephrotic syndrom* or neuromuscular or non-hodgkin* or nonhodgkin* or "multiple sclerosis" or myeloma or myocarditis or myocardiopath* or myopath* or (myocardi* near (deteri* or disease* or disorder* or syndrom* or manifestation*)) or "nephrotic syndrome" or ((neurodegenerat* or neuro-degenerat) near (disease* or disorder* or syndrom)) or ((nutritional or metabolic) near (disease* or disorder* or syndrom*)) or

((organ* or kidney or "stem cell") near (transplant* or recipient*)) or ("nervous system" near (disease* or disorder* or syndrom*)) or (neurological near (condition* or disease* or disorder* or syndrom*)) or neuropath* or neurosarcoido* or occlusion* or obesity or obese or orthopedic* or orthopaedic* or ((esophageal or oesophageal) near (disease* or disorder* or syndrom*)) or ((oral or mouth) near (disease* or disorder* or syndrom* or manifestation*)) or osteo* or "otitis media" or otorhinolaryngolog* or otosclerosis or (pancrea* near (disease* or disorder* or syndrom*)) or papulosquamous or paraplegi* or parkinson* or (peripheral near (arterial or vascular or disease* or disorder* or syndrom*)) or (peritoneal near (disease* or disorder* or syndrom*)) or photodermato* or "pick disease*" or pneumo* or polio* or polyp* or polydipsia or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or porphyrias or (pregnancy near complicat*) or "premature aging" or proteostasis or pseudophakia or psoriasis or parapsoriasis or prolapse or (pulmonary near (disease* or disorder* or syndrom*)) or purpur* or (recurren* near (abortion* or miscarr*)) or ((rectum or rectal) near (disease* or disorder* or syndrom*)) or ((renal or kidney) near (disease* or disorder* or failure or syndrom*)) or (respiratory near (disease* or disorder* or syndrom*)) or reticulocytosis or retinopathy or rheumat* or ricket* or sarcoido* or sepsis or septic* or seizure* or sclerosis or scoliosis or "sickle cell" or ((sjogren* or sjoegren* or sicca*) near (syndrom* or disease* or disorder*)) or ((skin or "connective tissue") near (disease* or disorder* or syndrom*)) or "sleep disorder*" or "sleep apnea" or "sleep apnoea" or insomnia* or dyssomnia* or hypersomnia* or "spina bifida" or "muscular atropy" or "short stature*" or "short bowel syndrom*" or (spin* near (degenerat* or disease* or disorder* or syndrom*)) or (spleen* near (disease* or disorder* or syndrom*)) or spondylo* or stenosis* or stoma* or (stomach near (disease* or disorder* or syndrom*)) or stroke or strokes or "cerebral infarct*" or tetraplegi* or thyroiditis* or (thyroid* near (disease* or disorder* or dysfunction* or syndrom*)) or ((tooth or teeth or enamel) near (decay* or discolo* or disease* or disorder* or dysfunction* or syndrom*)) or "tropical sprue" or tuberculosis or (systemic near (disorder* or disease* or syndrom*)) or thrombocyto* or tremor or tremors or (turner* near (syndrome* or disease* or disorder*)) or ulcer* or (urogenital near (disease* or disorder* or syndrom*)) or vasculopath* or (vascular near (disease* or disorder* or occlu* or syndrom*)) or vestibular or ((virus or viral or bacteri* or parasit*) near (infection* or disease*)) or (wasting near (disorder* or disease* or syndrom*)) or (whipple near (disorder* or disease* or syndrom*)) or (william* near (syndrom* or disease* or disorder*)) or zoster*)) (13,693,359)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#8 (#7 and #1) (5889)
#7 (#6 OR #5 OR #4 OR #3 OR #2) (6,827,636)
#6 (TS=("clinical decision making" or "logistic model*" or "statistical model*")) (81,189)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#5 (TS=((multivaria* or multicomponent*) NEAR (model* or algorithm* or score or scores or scoring or rule or rules or index or tool or tools or panel or criteri*))) (156,496)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#4 (TS=(clinic* NEAR (model* or algorithm* or score or scores or scoring or risk or risks or rule or rules or predict* or index or tool or tools or panel or criteri* or decision* or stratif* or diagnos* or detect* or identif* or probabilit*))) (1,061,406)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#3 (TS=((detect* or diagnos* or identif* or decision* or predict* or prognos* or stratif* or validat*) NEAR (risk or risks or model* or factor* or algorithm* or score or scores or scoring or system or technique* or aid or aids or rule or rules or index or variable* or tool or tools or panel or criteri* or characteristic* or history or finding* or value* or assay or stratif* or biomarker*))) (5,481,423)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#2 (TS=((detect* or diagnos* or identif* or decision* or predict* or prognos* or risk or risks or stratif* or validat*) NEAR (model* or factor* or algorithm* or score or scores or scoring or system or technique* or aid or aids or rule or rules or index or variable* or tool or tools or panel or criteri* or characteristic* or history or finding* or value* or assay or stratif* or biomarker*))) (6,133,858)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020
#1 TS=((celiac* OR coeliac*) NEAR (asymptomatic OR atypical OR adolesc* OR adult* OR cases OR cohort* OR child* OR disease* OR disorder* OR family OR families OR familial OR "genetic

predispos*" OR "genetic pre-dispos*" OR heredit* OR infant* OR men OR patient* OR people OR population* OR subjects OR symptomatic OR syndrom* OR sprue OR women))) NOT (TS=((celiac* OR coeliac*) NEAR (angiography OR artery OR arteries OR axis OR plexus OR trunk))) (25,557) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2020

Appendix 2 Flow diagram

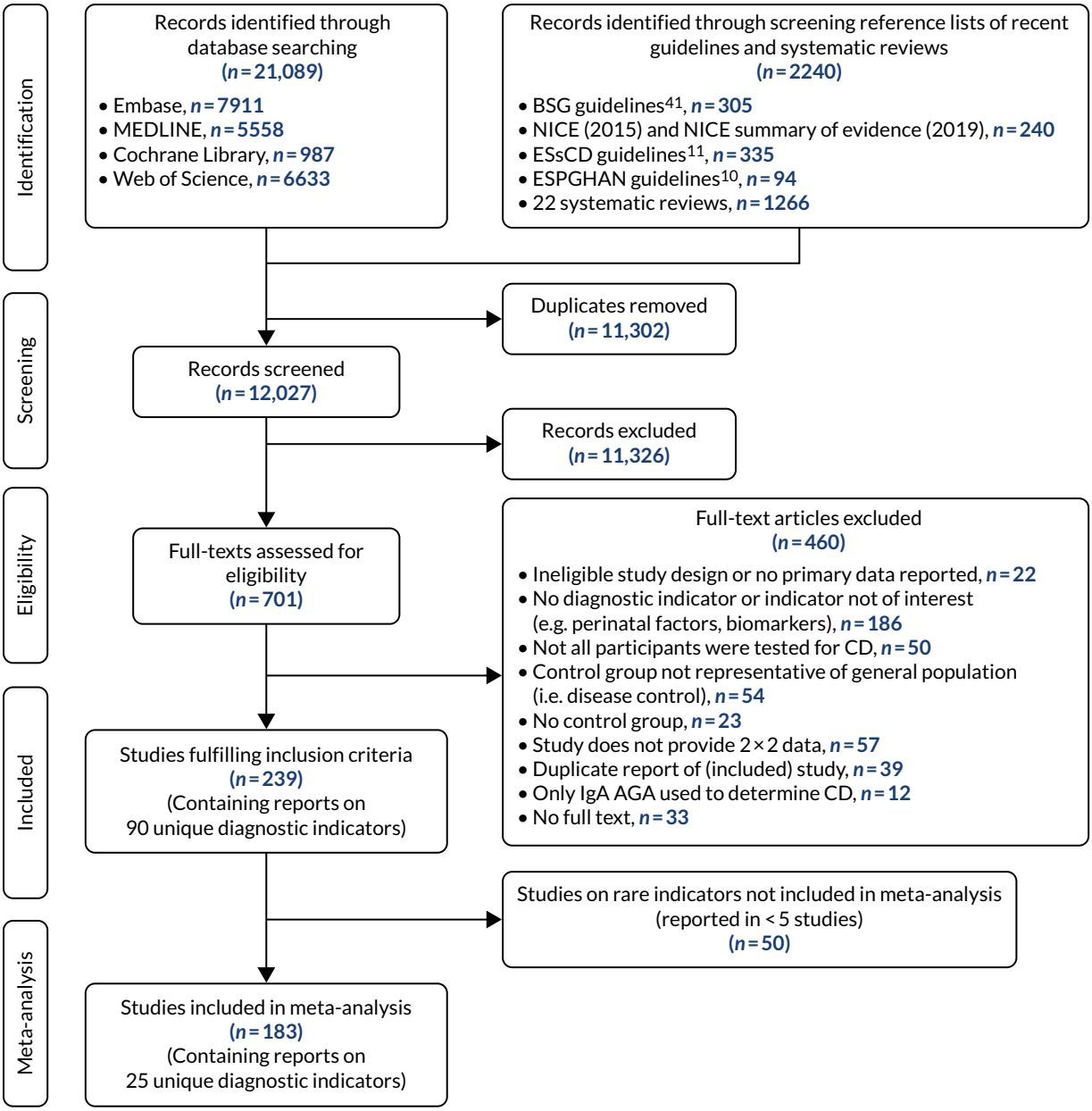

FIGURE 26 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. BSG guidelines,[41] ESsCD guidelines,[11] ESPGHAN guidelines.[10] AGA, anti-gliadin antibodies; BSG, British Society of Gastroenterology.

Appendix 3 Study characteristics

TABLE 25 Summary table of study characteristics

Diagnostic indicator	Diagnostic indicator details	Studies (*n*)	Total sample (*n*)	CD patients (*n*)	Age groups	Study designs	Control groups	Reference standards (CD diagnosis strategy)
Symptoms								
Abdominal pain	(Recurrent or acute) abdominal or stomach pain	12	48,451	1014	• Adults, *n* = 6 • Children, *n* = 6	• Case–control (DI),[a] *n* = 3 • Nested case–control (CD), *n* = 2 • Cohort/cross-sectional, *n* = 7	• Healthy controls, *n* = 3 • Population sample without diagnostic indicator, *n* = 9	• Serology only, *n* = 8 • Biopsy ± serology, *n* = 4
Acid reflux symptoms	Dyspepsia, functional dyspepsia, gastro-oesophageal reflux symptoms, heartburn	10	12,192	534	• Adults, *n* = 9 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 3 • Nested case–control (DI),[a] *n* = 2 • Nested case–control (CD), *n* = 1 • Cohort/cross-sectional, *n* = 4	• Healthy controls, *n* = 3 • Population sample without diagnostic indicator, *n* = 7	• Serology only, *n* = 6 • Biopsy ± serology, *n* = 4
Bloating or abdominal distension	Bloating, abdominal distension	6	32,694	624	• Adults, *n* = 4 • Children, *n* = 2	• Nested case–control (CD), *n* = 1 • Cohort/cross-sectional, *n* = 5	• Population sample without diagnostic indicator, *n* = 6	• Serology only, *n* = 4 • Biopsy ± serology, *n* = 2
Constipation	(Chronic) constipation	12	54,286	943	• Adults, *n* = 5 • Children, *n* = 7	• Case–control (DI)[a], *n* = 1 • Nested case–control (DI),[a] *n* = 1 • Nested case–control (CD),[b] *n* = 1 • Cohort/cross-sectional, *n* = 9	• Healthy controls, *n* = 1 • Population sample without diagnostic indicator, *n* = 11	• Serology only, *n* = 8 • Biopsy ± serology, *n* = 4
Diarrhoea	Diarrhoea	13	55,500	1126	• Adults, *n* = 7 • Children, *n* = 6	• Case–control (DI),[a] *n* = 1 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 10	• Healthy controls, *n* = 1 • Population sample without diagnostic indicator, *n* = 12	• Serology only, *n* = 10 • Biopsy ± serology, *n* = 3

Diagnostic indicator	Diagnostic indicator details	Studies (*n*)	Total sample (*n*)	CD patients (*n*)	Age groups	Study designs	Control groups	Reference standards (CD diagnosis strategy)
Vomiting and nausea	Vomiting, nausea, nausea after eating	7	44,937	435	• Adults, *n* = 3 • Children, *n* = 4	• Cohort/cross-sectional, *n* = 7	• Population sample without diagnostic indicator, *n* = 7	• Serology only, *n* = 6 • Biopsy ± serology, *n* = 1
Weight loss	Weight loss	5	31,739		• Adults, *n* = 3 • Children, *n* = 2	• Nested case–control (CD), *n* = 2 • Cohort/cross-sectional, *n* = 3	• Population sample without diagnostic indicator, *n* = 5	• Serology only, *n* = 4 • Biopsy ± serology, *n* = 1
Risk conditions								
Anaemia	IDA, low haemoglobin levels, pernicious anaemia of obscure origin or unspecified	17	13,477	715	• Adults, *n* = 13 • Children, *n* = 4	• Case–control (DI),[a] *n* = 9 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 6	• Healthy controls, *n* = 8 • Population sample without diagnostic indicator, *n* = 9	• Serology only, *n* = 9 • Biopsy ± serology, *n* = 8
Arthritis	RA, AS, juvenile idiopathic arthritis, psoriatic arthritis, juvenile rheumatic diseases	15	10,745	542	• Adults, *n* = 8 • Children, *n* = 5 Mixed, *n* = 2	• Case–control (DI),[a] *n* = 11 • Nested case–control (CD),[b] *n* = 1 • Cohort/cross-sectional, *n* = 3	• Healthy controls, *n* = 13 • Population sample without diagnostic indicator, *n* = 2	• Serology only, *n* = 7 • Biopsy ± serology, *n* = 8
Chronic liver disease	Hepatic disease, hepatitis, PBC (unexplained) abnormal liver enzymes, ALD, chronic hepatitis C	15	8682	448	• Adults, *n* = 9 • Children, *n* = 2 • Mixed, *n* = 4	• Case–control (DI),[a] *n* = 12 • Nested case–control (CD),[b] *n* = 1 • Cohort/cross-sectional, *n* = 2	• Healthy controls, *n* = 12 • Population sample without diagnostic indicator, *n* = 3	• Serology only, *n* = 7 • Biopsy ± serology, *n* = 8
Dermatitis herpetiformis	Dermatitis herpetiformis	5	1429	579	• Adults, *n* = 4 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 3 • Nested case–control (CD),[b] *n* = 2	• Healthy controls, *n* = 3 • Population sample without diagnostic indicator, *n* = 2	• Serology only, *n* = 4 • Biopsy ± serology, *n* = 1

continued

TABLE 25 Summary table of study characteristics (*continued*)

Diagnostic indicator	Diagnostic indicator details	Studies (*n*)	Total sample (*n*)	CD patients (*n*)	Age groups	Study designs	Control groups	Reference standards (CD diagnosis strategy)
Epilepsy	Epilepsy, ataxia	12	10,717	505	• Adults, *n* = 2 • Children, *n* = 9 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 11 • Nested case–control (CD),[b] *n* = 1	• Healthy controls, *n* = 11 • Population sample without diagnostic indicator, *n* = 1	• Serology only, *n* = 5 • Biopsy ± serology, *n* = 7
Fracture	Vertebra fracture, wrist fracture, fractures (unspecified)	8	24,741	549	Adults, *n* = 8	• Case–control (DI),[a] *n* = 3 • Nested case–control (CD),[b] *n* = 1 • Cohort/cross-sectional, *n* = 4	• Healthy controls, *n* = 3 • Population sample without diagnostic indicator, *n* = 5	• Serology only, *n* = 7 • Biopsy ± serology, *n* = 1
Inflammatory bowel disease	Ulcerative colitis, Crohn's disease	6	2886	32	• Adults, *n* = 4 • Children, *n* = 1 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 6	• Healthy controls, *n* = 6	• Serology only, *n* = 3 • Biopsy ± serology, *n* = 3
IBS	IBS, functional GI disorder	18	18,446	842	• Adults, *n* = 17 • Children, *n* = 1	• Case–control (DI),[a] *n* = 12 • Nested case–control (DI),[a] *n* = 1 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 3	• Healthy controls, *n* = 12 • Population sample without diagnostic indicator, *n* = 6	• Serology only, *n* = 11 • Biopsy ± serology, *n* = 7
Migraine	Migraine	5	2478	42	• Adults, *n* = 1 • Children, *n* = 4	• Case–control (DI),[a] *n* = 5	• Healthy controls, *n* = 5	• Serology only, *n* = 2 • Biopsy ± serology, *n* = 3
Multiple sclerosis	Multiple sclerosis	5	1086	12	• Adults, *n* = 4 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 5	• Healthy controls, *n* = 5	• Serology only, *n* = 4 • Biopsy ± serology, *n* = 1

Diagnostic indicator	Diagnostic indicator details	Studies (*n*)	Total sample (*n*)	CD patients (*n*)	Age groups	Study designs	Control groups	Reference standards (CD diagnosis strategy)
Osteoporosis	Osteoporosis	9	20,218	962	• Adults, *n* = 8 • Mixed, *n* = 1	• Case–control (DI),[a] *n* = 4 • Case–control (CD),[b] *n* = 1 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 2	• Healthy controls, *n* = 4 • Population sample without diagnostic indicator, *n* = 5	• Serology only, *n* = 6 • Biopsy ± serology, *n* = 3
Psoriasis	Psoriasis	6	1127	44	• Adults, *n* = 3 • Mixed, *n* = 3	• Case–control (DI),[a] *n* = 6	• Healthy controls, *n* = 5 • Population sample without diagnostic indicator, *n* = 1	• Serology only, *n* = 4 • Biopsy ± serology, *n* = 2
Subfertility or recurrent pregnancy loss	Idiopathic or immunological infertility; previous or recurrent miscarriages, or implantation failure	16	12,690	808	• Adults, *n* = 16	• Case–control (DI),[a] *n* = 12 • Nested case–control (DI),[a] *n* = 1 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 1	• Healthy controls, *n* = 12 • Population sample without diagnostic indicator, *n* = 4	• Serology only, *n* = 12 • Biopsy ± serology, *n* = 4
Systemic lupus erythematosus	Systemic lupus erythematosus	6	1004	9	• Adults, *n* = 5 • Children, *n* = 1	• Case–control (DI),[a] *n* = 5 • Cohort/cross-sectional, *n* = 1	• Healthy controls, *n* = 6	• Serology only, *n* = 2 • Biopsy ± serology, *n* = 4
Thyroid disease	Autoimmune thyroid disease, Graves' disease, Hashimoto's thyroiditis	23	27,031	1083	• Adults, *n* = 16 • Children, *n* = 5 • Mixed, *n* = 2	• Case–control (DI),[a] *n* = 15 • Nested case–control (DI),[a] *n* = 2 • Nested case–control (CD),[b] *n* = 2 • Cohort/cross-sectional, *n* = 4	• Healthy controls, *n* = 15 • Population sample without diagnostic indicator, *n* = 8	• Serology only, *n* = 13 • Biopsy ± serology, *n* = 10

continued

TABLE 25 Summary table of study characteristics (*continued*)

Diagnostic indicator	Diagnostic indicator details	Studies (*n*)	Total sample (*n*)	CD patients (*n*)	Age groups	Study designs	Control groups	Reference standards (CD diagnosis strategy)
Type 1 diabetes	Type 1 diabetes	31	26,635	1349	• Adults, $n = 11$ • Children, $n = 12$ • Mixed, $n = 8$	• Case–control (DI),[a] $n = 28$ • Nested case–control (CD),[b] $n = 1$ • Cohort/cross-sectional, $n = 2$	• Healthy controls, $n = 27$ • Population sample without diagnostic indicator, $n = 4$	• Serology only, $n = 17$ • Biopsy ± serology, $n = 14$
Type 2 diabetes	Type 2 diabetes	6	8199	110	• Adults, $n = 4$ • Mixed, $n = 2$	• Case–control (DI),[a] $n = 5$ • Cohort/cross-sectional, $n = 1$	• Healthy controls, $n = 5$ • Population sample without diagnostic indicator, $n = 1$	• Serology only, $n = 5$ • Biopsy ± serology, $n = 1$
Family history								
Family history of CD	Relatives with CD (first or second degree, or unspecified)	13	31,827	672	• Adults, $n = 5$ • Children, $n = 4$ • Mixed, $n = 4$	• Case–control (DI),[a] $n = 6$ • Case–control (CD),[b] $n = 1$ • Nested case–control (DI),[a] $n = 1$ • Cohort/cross-sectional, $n = 5$	• Healthy controls, $n = 6$ • Population sample without diagnostic indicator, $n = 7$	• Serology only, $n = 12$ • Biopsy ± serology, $n = 1$

ALD, alcoholic liver disease; AS, ankylosing spondylitis; DI, diagnostic indicator; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis.

a (Nested) case–control (DI): (nested) case–control studies in which cases were recruited based on having the DI. 'Nested' case–control studies are nested within a cohort, whereby cases and controls are selected from the same cohort.

b (Nested) case–control (CD): (nested) case–control studies in which cases were recruited based on having CD.

Appendix 4 Study characteristics per diagnostic indicator

TABLE 26 Study characteristic: abdominal pain

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Acute abdominal pain	600	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	NR	Hopper *et al.*[286]
Adults	Case–control (DI)	Acute abdominal pain	600	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	UK	Sanders *et al.*[287]
Adults	Cohort	Abdominal pain	3196	NR	People without abdominal pain	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Abdominal pain	2976	51–75	People without abdominal pain	Serology and only positive patients biopsied	Community	Brazil	Oliveira *et al.*[289]
Adults	Nested case–control (CD)	Recurrent abdominal pain	800	51–75	People without recurrent abdominal pain	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Abdominal pain	381	51–75	People without abdominal pain	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Children	Case–control (DI)	Recurrent abdominal pain	173	51–75	Healthy controls	EMA positive	Primary	Canada	Fitzpatrick *et al.*[291]
Children	Cohort	Any stomach pains	4327	NR	Children without stomach pains	Double positive for two antibodies	Community	UK	Bingley *et al.*[2]
Children	Cohort	Abdominal pain	18,672	51–75	Children without abdominal pain	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Abdominal pain	3093	26–50	Children without abdominal pain	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Cohort	Abdominal pain	3715	26–50	Children without abdominal pain	tTG positive	Community	The Netherlands	Wahab *et al.*[180]
Children	Cohort	Stomach aches	9918	51–75	Children without stomach aches	tTG positive	Secondary	USA	Stahl *et al.*[293]

DI, diagnostic indicator; NR, not reported.

TABLE 27 Study characteristic: acid reflux symptoms

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Dyspepsia	640	51–75	Healthy controls	Other	Secondary	Argentina	Lasa *et al.*[294]
Adults	Case–control (DI)	Dyspepsia	105	NR	Healthy controls	All patients biopsied – no serology	NR	NR	Lecleire *et al.*[295]
Adults	Cohort	Dyspepsia	3118	NR	People without dyspepsia	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Heartburn	3847	51–75	People without heartburn	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Adults	Cohort	Dyspepsia	427	1–25	Healthy controls	Serology and only positive patients biopsied	Unclear	Mexico	Lara-Carmona *et al.*[297]
Adults	Cohort	Heartburn	1886	NR	People without heartburn	Other	Primary	Finland	Tikkakoski *et al.*[298]
Adults	Nested case–control (CD)	Dyspepsia	800	51–75	People without dyspepsia	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (DI)	Gastro-oesophageal reflux symptoms	1000	51–75	People without gastro-oesophageal reflux symptoms	Serology and all patients biopsied	Community	Sweden	Ludvigsson *et al.*[299]
Adults	Nested case–control (DI)	Dyspepsia	112	26–50	Healthy controls	tTG positive	Community	USA	Locke *et al.*[300]
Mixed	Case–control (DI)	Functional dyspepsia	257	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Spain	Vivas *et al.*[301]

DI, diagnostic indicator; NR, not reported.

TABLE 28 Study characteristic: anaemia

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Low haemoglobin levels	174	NR	People with normal haemoglobin levels	tTG positive	Unclear	USA	Alexander *et al.*[302]
Adults	Case–control (DI)	IDA of obscure origin	321	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	India	Javid *et al.*[303]
Adults	Case–control (DI)	IDA of obscure origin	196	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Uçardağ *et al.*[304]
Adults	Case–control (DI)	IDA	268	51–75	Healthy controls	Serology and all patients biopsied	Secondary/ community	Argentina	Lasa *et al.*[305]
Adults	Case–control (DI)	IDA	97	51–75	Healthy controls	tTG positive	Secondary	Türkiye	Cikrikcioglu *et al.*[306]
Adults	Case–control (DI)	Pernicious anaemia	165	51–75	Healthy controls	EMA positive	Unclear	Poland	Morawiec-Szymonik *et al.*[307]
Adults	Cohort	Anaemia	982	NR	People without anaemia	Serology and only positive patients biopsied	Primary	UK	Ransford *et al.*[308]
Adults	Cohort	Anaemia	1197	26–50	People without anaemia	Double positive for two antibodies	Community	The United Arab Emirates	Abu-Zeid *et al.*[277]
Adults	Cohort	IDA	1200	62.8	People without anaemia	Serology and only positive patients biopsied	Primary	UK	Sanders *et al.*[309]

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Anaemia/IDA	527	51–75	People without anaemia	Double positive for two antibodies	Secondary	Malaysia	Yap *et al.*[276]
Adults	Cohort	Anaemia	5060	100	People without anaemia	Double positive for two antibodies	Secondary	Italy	Greco *et al.*[310]
Adults	Nested case–control (CD)	Anaemia	800	51–75	People without anaemia	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Anaemia	381	51–75	People without anaemia	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Children	Case–control (DI)	IDA	358	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Kalayci *et al.*[311]
Children	Case–control (DI)	IDA	184	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Islamic Republic of Iran	Shahriari *et al.*[312]
Children	Case–control (DI)	IDA	304	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	India	Narang *et al.*[313]
Children	Cohort	IDA	1263	26–50	Children without IDA	tTG positive	Community	Türkiye	Ertekin *et al.*[314]

DI, diagnostic indicator; NR, not reported.

TABLE 29 Study characteristic: arthritis

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	RA	220	NR	Healthy controls	Serology and only positive patients biopsied	Unclear	Italy	Bizzaro *et al.*[315]
Adults	Case–control (DI)	RA	83	NR	Healthy controls	EMA positive	Secondary	Ireland	Feighery *et al.*[316]
Adults	Case–control (DI)	RA	182	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Brazil	Nisihara *et al.*[317]
Adults	Case–control (DI)	Arthritis (PsA, RA or AS)	237	26–50	Healthy controls	Double positive for two antibodies	Secondary	Italy	Picarelli *et al.*[318]
Adults	Case–control (DI)	Arthritis (PsA, RA or AS)	275	26–50	Healthy controls	tTG positive	Secondary	Italy	Riente *et al.*[319]
Adults	Cohort	RA	100	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Luft *et al.*[320]
Adults	Cohort	RA	6919	51–75	People without RA	Double positive for two antibodies	Community	Finland	Heikkilä *et al.*[321]
Adults	Nested case–control (CD)	RA	800	51–75	People without RA	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Children	Case–control (DI)	Juvenile rheumatic diseases	90	51–75	Healthy controls	tTG positive	Secondary	Egypt	Gheita *et al.*[322]
Children	Case–control (DI)	Juvenile idiopathic arthritis	181	51–75	Healthy controls	Serology and only positive patients biopsied	Unclear	Türkiye	Sahin *et al.*[323]

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Children	Case–control (DI)	Juvenile idiopathic arthritis	205	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Austria	Skrabl-Baumgartner *et al.*[324]
Children	Case–control (DI)	Juvenile idiopathic arthritis	309	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Stagi *et al.*[325]
Children	Cohort	Juvenile idiopathic arthritis	70	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Brazil	Robazzi *et al.*[326]
Mixed	Case–control (DI)	Juvenile idiopathic arthritis	1025	NR	Healthy controls	tTG positive	Secondary	USA	Taneja *et al.*[327]
Mixed	Case–control (DI)	AS	49	1–25	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Toğrol *et al.*[328]

AS, ankylosing spondylitis; DI, diagnostic indicator; NR, not reported; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

TABLE 30 Study characteristic: bloating or abdominal distension

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Bloating	1830	NR	People without bloating	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Bloating	3847	51–75	People without bloating	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Adults	Cohort	Bloating	1886	NR	People without bloating	Other	Primary	Finland	Tikkakoski *et al.*[298]
Adults	Nested case–control (CD)	Bloating	800	51–75	People without bloating	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Children	Cohort	Abdominal distension	18,598	51–75	Children without abdominal distension	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Abdominal distension	5733	26–50	People without abdominal extension	Serology and only positive patients biopsied	Community	Italy	Nenna *et al.*[329]

NR, not reported.

TABLE 31 Study characteristic: constipation

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Constipation	3196	NR	People without constipation	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Constipation	2976	51–75	People without constipation	Serology and only positive patients biopsied	Community	Brazil	Oliveira *et al.*[289]
Adults	Cohort	Constipation	3847	51–75	People without constipation	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Adults	Cohort	Constipation	1886	NR	People without constipation	Other	Primary	Finland	Tikkakoski *et al.*[298]
Adults	Nested case–control (CD)	Constipation	800	51–75	People without constipation	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Children	Case–control (DI)	Chronic constipation	1303	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Çakir *et al.*[330]
Children	Cohort	Constipation	4327	NR	Children without constipation	Double positive for two antibodies	Community	UK	Bingley *et al.*[2]
Children	Cohort	Constipation	18,576	51–75	Children without constipation	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Constipation	3120	26–50	Children without constipation	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Cohort	Constipation	3715	26–50	Children without constipation	tTG positive	Community	The Netherlands	Wahab *et al.*[180]
Children	Cohort	Constipation	9918	51–75	Children without constipation	tTG positive	Secondary	USA	Stahl *et al.*[293]
Children	Nested case–control (DI)	Functional constipation	622	NR	Children without functional GI disorders	Serology and only positive patients biopsied	Community	Colombia	Fifi *et al.*[331]

DI, diagnostic indicator; NR, not reported.

TABLE 32 Study characteristic: dermatitis herpetiformis

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Dermatitis herpetiformis	150	NR	Healthy controls	Double positive for two antibodies	Secondary	Poland	Kumar *et al.*[332]
Adults	Case–control (DI)	Dermatitis herpetiformis	46	NR	Healthy controls	Other	Secondary	Bulgaria	Velikova *et al.*[333]
Adults	Nested case–control (CD)	Dermatitis herpetiformis	381	51–75	People without dermatitis herpetiformis	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Adults	Nested case–control (CD)	Dermatitis herpetiformis	800	51–75	People without dermatitis herpetiformis	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Mixed	Case–control (DI)	Dermatitis herpetiformis	52	26–50	Controls	Serology and all patients biopsied	Secondary	Argentina	Smecuol *et al.*[334]

DI, diagnostic indicator; NR, not reported.

TABLE 33 Study characteristic: diarrhoea

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Diarrhoea	1197	26–50	People without diarrhoea	Double positive for two antibodies	Community	The United Arab Emirates	Abu-Zeid *et al.*[277]
Adults	Cohort	Diarrhoea	3186	NR	People without diarrhoea	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Diarrhoea	2976	51–75	People without diarrhoea	Serology and only positive patients biopsied	Community	Brazil	Oliveira *et al.*[289]
Adults	Cohort	Diarrhoea	3847	51–75	People without diarrhoea	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Adults	Cohort	Diarrhoea	1886	NR	People without diarrhoea	Other	Primary	Finland	Tikkakoski *et al.*[298]
Adults	Nested case–control (CD)	Diarrhoea	800	51–75	People without diarrhoea	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Diarrhoea	381	51–75	People without diarrhoea	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Children	Case–control (DI)	Diarrhoea	1650	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Islamic Republic of Iran	Imanzadeh *et al.*[335]
Children	Cohort	Diarrhoea	4327	NR	Children without diarrhoea	Double positive for two antibodies	Community	UK	Bingley *et al.*[2]
Children	Cohort	Diarrhoea	18,602	51–75	Children without diarrhoea	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Diarrhoea	3015	26–50	Children without diarrhoea	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Cohort	Diarrhoea	3715	26–50	Children without diarrhoea	tTG positive	Community	The Netherlands	Wahab *et al.*[180]
Children	Cohort	Diarrhoea	9918	51–75	Children without diarrhoea	tTG positive	Secondary	USA	Stahl *et al.*[293]

DI, diagnostic indicator; NR, not reported.

TABLE 34 Study characteristic: epilepsy

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Epilepsy	1427	51–75	Healthy controls	tTG positive	Community	Finland	Ranua *et al.*[336]
Adults	Nested case–control (CD)	Epilepsy/ataxia	800	51–75	People without epilepsy/ataxia	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Children	Case–control (DI)	Epilepsy	535	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Greece	Mavroudi *et al.*[337]
Children	Case–control (DI)	Epilepsy	535	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Greece	Mavroudi *et al.*[337]
Children	Case–control (DI)	Epilepsy	273	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Dalgiç *et al.*[338]
Children	Case–control (DI)	Epilepsy	190	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Dai *et al.*[339]
Children	Case–control (DI)	Epilepsy	275	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Serbia	Djurić *et al.*[340]
Children	Case–control (DI)	Epilepsy	572	26–50	Healthy controls	tTG positive	Secondary	Italy	Giordano *et al.*[341]
Children	Case–control (DI)	Epilepsy	380	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Işikay *et al.*[342]
Children	Case–control (DI)	Epilepsy	1000	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Işıkay *et al.*[343]
Children	Case–control (DI)	Epilepsy	70	26–50	Healthy controls	EMA positive	Secondary	Israel	Lahat *et al.*[344]
Mixed	Case–control (DI)	Epilepsy	4660	26–50	Healthy controls	EMA positive	Secondary	Brazil	Pratesi *et al.*[345]

DI, diagnostic indicator.

TABLE 35 Study characteristic: family history of CD

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	CD in family	334	NR	Healthy controls	tTG positive	Secondary	India	Soni *et al.*[346]
Adults	Cohort	FDRs with CD	1197	26–50	People without FDRs with CD	Double positive for two antibodies	Community	The United Arab Emirates	Abu-Zeid *et al.*[277]
Adults	Cohort	CD in family	527	51–75	People without a family history of CD	Double positive for two antibodies	Secondary	Malaysia	Yap *et al.*[276]
Adults	Nested case–control (DI)	FDRs with CD	2128	NR	People without CD in family	tTG positive	Community	USA	Choung *et al.*[347]
Adults	Case–control (DI)	FDRs with CD	6059	51–75	Healthy controls	EMA positive	Community/ secondary	USA	Fasano *et al.*[348]
Children	Cohort	CD in family	3768	51–75	People without family history of CD	Serology and only positive patients biopsied	Community	Cyprus	Beser *et al.*[349]
Children	Cohort	CD in family	4308	26–50	Children without CD in family	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Case–control (DI)	FDRs with CD	2575	51–75	Healthy controls	EMA positive	Community/ secondary	USA	Fasano *et al.*[348]
Children	Cohort	FDRs with CD	9973	51–75	Children without a FDR with CD	tTG positive	Secondary	USA	Stahl *et al.*[293]
Mixed	Case–control (DI and CD)	FDRs with CD	114	NR	Healthy controls	tTG positive	Unclear	Cuba	Cintando *et al.*[350]
Mixed	Case–control (DI)	FDRs with CD	241	51–75	Healthy controls	EMA positive	Secondary	Brazil	Kotze *et al.*[351]
Mixed	Case–control (DI)	FDRs and SDRs with CD	333	51–75	Healthy controls	Double positive for two antibodies	Unclear	Brazil	Nass *et al.*[352]
Mixed	Case–control (DI)	FDRs and SDRs with CD	270	26–50	Healthy controls	Double positive for two antibodies	Unclear	Portugal	Utiyama *et al.*[353]

DI, diagnostic indicator; FDR, first-degree relative; NR, not reported; SDR, second-degree relative.

TABLE 36 Study characteristic: fracture

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Acute distal radius or ankle fracture	597	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Norway	Hjelle *et al.*[354]
Adults	Case–control (DI)	Acute distal radius or ankle fracture	228	76–100	Healthy controls	tTG positive	Secondary	Norway	Hjelle *et al.*[355]
Adults	Case–control (DI)	Hip fracture	208	100	Women without osteoporosis admitted for elective hip joint replacement	tTG positive	Community	USA	LeBoff *et al.*[356]
Adults	Cohort	Non-traumatic fractures	2121	51–75	Healthy controls	tTG positive	Community	Australia	Potter *et al.*[357]
Adults	Cohort	Fracture	6480	100	Women without fractures	tTG positive	Community	Sweden	Agardh *et al.*[358]
Adults	Cohort	Vertebra fracture	6919	51–75	People without vertebra fracture	Double positive for two antibodies	Community	Finland	Heikkilä *et al.*[321]
Adults	Cohort	Fracture of the wrist	7345	51–75	People without wrist fracture	EMA positive	Primary	UK	West *et al.*[359]
Adults	Nested case–control (CD)	Fracture	843	51–75	People without fractures	Double positive for two antibodies	Community	USA	Choung *et al.*[360]

DI, diagnostic indicator.

TABLE 37 Study characteristic: HLA

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Nested case–control (CD)	*HLA-DQ2*	97	NR	Healthy controls	Serology and all patients biopsied	Secondary	Sweden	Walker *et al.*[361]
Children	Case–control (CD)	*HLA-DQ2*, *HLA-DQ8* or both	1320	51–75	Children without risk genotype	Serology and only positive patients biopsied	Secondary	Sweden	Sandström *et al.*[179]
Children	Cohort	*HLA-DQ2*, *HLA-DQ8* or both	2781	26–50	People without risk genotype	tTG positive	Community	The Netherlands	Beth *et al.*[181]
Children	Cohort	*HLA-DQ2*, *HLA-DQ8* or both	4308	26–50	Children without risk genotype	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Cohort	*HLA-DQ2.2*, *HLA-DQ2.5* or *HLA-DQ8*	3715	26–50	Children without risk genotype	tTG positive	Community	The Netherlands	Wahab *et al.*[180]
Children	Cohort	*HLA-DR4-DQ8*, *HLA-DR3-DQ2* or both	3627	51–75	Children not carrying *HLA-DR3-DQ2* or *HLA-DR4-DQ8*	Serology and only positive patients biopsied	Community	Finland	Mäki *et al.*[178]
Children	Nested case–control (DI)	*HLA-DQ2*, *HLA-DQ8* or both	3435	26–50	Newborns without risk genotype	Serology and only positive patients biopsied	Community	Sweden	Björck *et al.*[177]
Mixed	Case–control (DI and CD)	*HLA-DQ2*	82	NR	CD patients and healthy controls without risk genotype	tTG positive	Unclear	Cuba	Cintado *et al.*[350]
Mixed	Case–control (CD)	*HLA-DQ2*	101	NR	People without *HLA-DQ2*	tTG positive	Secondary	Islamic Republic of Iraq	Khudher *et al.*[362]

DI, diagnostic indicator; NR, not reported.

TABLE 38 Study characteristic: inflammatory bowel disease

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Ulcerative colitis or Crohn's disease	865	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	UK	Horoldt *et al.*[363]
Adults	Case–control (DI)	Ulcerative colitis or Crohn's disease	955	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	UK	Leeds *et al.*[364]
Adults	Case–control (DI)	Ulcerative colitis or Crohn's disease	362	26–50	Healthy controls	Double positive for two antibodies	Secondary	Japan	Watanabe *et al.*[365]
Adults	Case–control (DI)	Ulcerative colitis or Crohn's disease	290	NR	Healthy controls	Serology and only positive patients biopsied	Unclear	Italy	Bizzero *et al.*[315]
Children	Case–control (DI)	Ulcerative colitis or Crohn's disease	328	26–50	Healthy controls	tTG positive	Secondary	NR	El-Matary *et al.*[366]
Mixed	Case–control (DI)	Ulcerative colitis	86	51–75	Healthy controls	EMA positive	Secondary	Estonia	Kull *et al.*[367]

DI, diagnostic indicator; NR, not reported.

TABLE 39 Study characteristic: IBS

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	IBS	233	76–100	Healthy controls	tTG positive	Secondary	Islamic Republic of Iran	Mehdi *et al.*[368]
Adults	Case–control (DI)	IBS	200	51–75	Healthy controls	tTG positive	Secondary	Poland	Respondek *et al.*[369]
Adults	Case–control (DI)	IBS	1064	76–100	Healthy controls	Double positive for two antibodies	Secondary	USA	Almazar *et al.*[370]
Adults	Case–control (DI)	IBS	950	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Cash *et al.*[371]
Adults	Case–control (DI)	IBS	68	51–75	Healthy controls	tTG positive	NR	Poland	Domżał-Magrowska *et al.*[372]
Adults	Case–control (DI)	IBS	492	51–75	Controls who underwent colonoscopy examination for colorectal cancer screening or polyp surveillance	tTG positive	Secondary	People's Republic of China	Kou *et al.*[373]
Adults	Case–control (DI)	IBS	1121	76–100	Healthy controls	Double positive for two antibodies	Secondary	USA	Saito-Loftus *et al.*[374]
Adults	Case–control (DI)	IBS	800	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Mexico	Sánchez-Vargas *et al.*[375]
Adults	Case–control (DI)	IBS	600	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	UK	Sanders *et al.*[376]
Adults	Case–control (DI)	IBS	678	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Mexico	Vargas *et al.*[377]

continued

TABLE 39 Study characteristic: IBS (*continued*)

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	IBS	758	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	People's Republic of China	Wang *et al.*[378]
Adults	Case–control (DI)	IBS	509	26–50	Healthy controls	tTG positive	Secondary	Saudi Arabia	Khayyat[379]
Adults	Cohort	IBS	1200	62.8	People without IBS	Serology and only positive patients biopsied	Primary	UK	Sanders *et al.*[309]
Adults	Cohort	IBS	3196	NR	People without IBS'	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Nested case–control (CD)	IBS	800	51–75	People without IBS	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	IBS	381	51–75	People without IBS	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Adults	Nested case–control (DI)	IBS	128	26–50	Healthy controls	tTG positive	Community	USA	Locke *et al.*[300]
Children	Cohort	Functional GI disorder	5268	NR	Healthy controls	Serology and only positive patients biopsied	Community	Sweden	Olen *et al.*[380]

DI, diagnostic indicator; NR, not reported.

TABLE 40 Study characteristic: chronic liver disease

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	PBC	168	NR	Healthy controls	Serology and only positive patients biopsied	Unclear	Italy	Bizarro *et al.*[315]
Adults	Case–control (DI)	PBC	162	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Greece	Chatzicostas *et al.*[381]
Adults	Case–control (DI)	Chronic hepatitis C	395	26–50	Healthy controls	Double positive for two antibodies	Secondary	Italy	Durante-Mangoni *et al.*[382]
Adults	Case–control (DI)	Chronic hepatitis C	275	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Hernandez *et al.*[383]
Adults	Case–control (DI)	ALD, HCV, PBC, PSC, CH	2002	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Sweden	Sjöberg *et al.*[384]
Adults	Case–control (DI)	Abnormal liver function tests	250	1–25	Healthy controls	tTG positive	Secondary	People's Republic of China	Yuan *et al.*[385]
Adults	Cohort	Hepatitis	1197	26–50	People without hepatitis	Double positive for two antibodies	Community	The United Arab Emirates	Abu-Zeid *et al.*[277]
Adults	Cohort	Hepatic diseases	527	51–75	People without hepatic diseases	Double positive for two antibodies	Secondary	Malaysia	Yap *et al.*[276]
Adults	Nested case–control (CD)	Unexplained abnormal levels of AST/ALT	800	51–75	People without unexplained abnormal AST/ALT	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]

continued

TABLE 40 Study characteristic: chronic liver disease (*continued*)

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Children	Case–control (DI)	Autoimmune hepatitis	46	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Egypt	El-Shabrawi *et al.*[386]
Children	Case–control (DI)	Autoimmune hepatitis	122	NR	Healthy controls	Serology and only positive patients biopsied	NR	Romania	Oana *et al.*[387]
Mixed	Case–control (DI)	HCV, HBV, AIH, PBC, PSC, NAFLD-ALD, NAFLD, and others	2084	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Greece	Germenis *et al.*[388]
Mixed	Case–control (DI)	Autoimmune hepatitis	167	NR	Healthy controls	Other	Secondary	Italy	Villalta *et al.*[389]
Mixed	Case–control (DI)	Chronic hepatitis C	267	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Spain	Vivas *et al.*[301]
Mixed	Case–control (DI)	Chronic hepatitis C	220	NR	Healthy controls	Other	Secondary	Italy	Villalta *et al.*[389]

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALT, alanine transaminase; AST, aspartate transaminase; CH, chronic hepatitis; DI, diagnostic indicator; HBV, chronic hepatitis B virus infection; HCV, chronic hepatitis C virus infection; NAFLD, non-alcoholic fatty liver disease; NR, not reported; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

TABLE 41 Study characteristic: migraine

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Migraine	326	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Gabrielli *et al.*[274]
Children	Case–control (DI)	Migraine	257	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Balci *et al.*[390]
Children	Case–control (DI)	Migraine	220	51–75	Healthy controls	tTG positive	Secondary	Türkiye	Alehan *et al.*[391]
Children	Case–control (DI)	Migraine	1600	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Islamic Republic of Iran	Inaloo *et al.*[392]
Children	Case–control (DI)	Migraine headaches	75	26–50	Healthy controls	EMA positive	Secondary	Israel	Lahat *et al.*[344]

DI, diagnostic indicator.

TABLE 42 Study characteristic: multiple sclerosis

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Multiple sclerosis	68	NR	Healthy controls	Serology and only positive patients biopsied	Unclear	Islamic Republic of Iran	Abolfazli *et al.*[393]
Adults	Case–control (DI)	Multiple sclerosis	417	51–75	Healthy controls	tTG positive	Secondary	Italy	Nicoletti *et al.*[394]
Adults	Case–control (DI)	Multiple sclerosis	195	76–100	Healthy controls	tTG positive	Secondary	Spain	Rodrigo *et al.*[395]
Adults	Case–control (DI)	Multiple sclerosis	185	51–75	Healthy controls	Double positive for two antibodies	Secondary	Sweden	Roth *et al.*[396]
Mixed	Case–control (DI)	Multiple sclerosis	221	51–75	Healthy controls	tTG positive	Secondary	Islamic Republic of Iran	Khoshbaten *et al.*[397]

DI, diagnostic indicator; NR, not reported.

TABLE 43 Study characteristic: osteoporosis

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Osteoporosis	197	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Brazil	Gusso *et al.*[398]
Adults	Case–control (DI)	Osteoporosis	560	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Islamic Republic of Iran	Shahbazkhani *et al.*[399]
Adults	Case–control (DI)	Osteoporosis	840	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Stenson *et al.*[400]
Adults	Case–control (DI)	Osteoporosis	1414	26–50	Healthy controls	Double positive for two antibodies	Secondary	Czechia	Vanciková *et al.*[401]
Adults	Cohort	Osteoporosis	2121	51–75	People without osteoporosis	tTG positive	Community	Australia	Potter *et al.*[357]
Adults	Cohort	Osteoporosis	6480	100	Women without osteoporosis	tTG positive	Community	Sweden	Agardh *et al.*[358]
Adults	Nested case–control (CD)	Osteoporosis	800	51–75	People without osteoporosis	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Osteoporosis	843	51–75	People without osteoporosis	Double positive for two antibodies	Community	USA	Choung *et al.*[360]
Mixed	Case–control (CD)	Osteoporosis	6963	NR	Patients without osteoporosis	Other	Secondary	USA	Shen *et al.*[402]

DI, diagnostic indicator; NR, not reported.

TABLE 44 Study characteristic: psoriasis

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Psoriasis	482	51–75	General population	Serology and only positive patients biopsied	Primary	Italy	De Bastiani *et al.*[403]
Adults	Case–control (DI)	Psoriasis	87	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Akbulut *et al.*[404]
Adults	Case–control (DI)	Chronic plaque psoriasis	160	26–50	Healthy controls	tTG positive	Unclear	India	Dhattarwal *et al.*[405]
Mixed	Case–control (DI)	Psoriasis	200	26–50	Healthy controls	tTG positive	Secondary	Italy	Montesu *et al.*[406]
Mixed	Case–control (DI)	Psoriasis	82	26–50	Healthy controls	tTG positive	Secondary	Egypt	Nagui *et al.*[407]
Mixed	Case–control (DI)	Psoriasis	116	26–50	Healthy controls	tTG positive	Secondary	India	Singh *et al.*[408]

DI, diagnostic indicator.

TABLE 45 Study characteristics: systemic lupus erythematosus

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Systemic lupus erythematosus	220	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Marai *et al.*[409]
Adults	Case–control (DI)	Systemic lupus erythematosus	220	NR	Healthy controls	Serology and only positive patients biopsied	Unclear	Italy	Bizzaro *et al.*[315]
Adults	Case–control (DI)	Systemic lupus erythematosus	76	NR	Healthy controls	EMA positive	Secondary	Ireland	Feighery *et al.*[316]
Adults	Case–control (DI)	Systemic lupus erythematosus	297	76–100	Healthy controls	Double positive for two antibodies	Secondary	Brazil	Picceli *et al.*[410]
Adults	Cohort	Systemic lupus erythematosus	100	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Luft *et al.*[320]
Children	Case–control (DI)	Systemic lupus erythematosus	91	76–100	Healthy controls	Serology and only positive patients biopsied	Unclear	Türkiye	Sahin *et al.*[411]

DI, diagnostic indicator; NR, not reported.

TABLE 46 Study characteristic: subfertility or recurrent pregnancy loss

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Recurrent miscarriages or implantation failure	528	100	Healthy controls	tTG positive	Secondary	Czechia	Cedíková *et al.*[412]
Adults	Case–control (DI)	Unexplained infertility or recurrent miscarriages	342	100	Healthy controls	tTG positive	Secondary	Mexico	Remes-Troche *et al.*[413]
Adults	Case–control (DI)	Recurrent miscarriages or implantation failure	279	100	Healthy controls	Serology and only positive patients biopsied	Secondary	Spain	Herraiz-Nicuesa *et al.*[414]
Adults	Case–control (DI)	Unexplained infertility	535	100	Healthy controls	tTG positive	Secondary	India	Kumar *et al.*[415]
Adults	Case–control (DI)	Recurrent pregnancy loss	808	100	Healthy controls	tTG positive	Secondary	USA	Kutteh *et al.*[416]
Adults	Case–control (DI)	Recurrent pregnancy loss	409	100	Healthy controls	tTG positive	Secondary	India	Kumar *et al.*[415]
Adults	Case–control (DI)	Recurrent pregnancy loss	86	100	Healthy controls	tTG positive	Secondary	Türkiye	Sarikaya *et al.*[417]
Adults	Case–control (DI)	Unexplained infertility	402	100	Healthy controls	Serology and only positive patients biopsied	Secondary	Israel	Shamaly *et al.*[418]
Adults	Case–control (DI)	Recurrent pregnancy loss	232	100	Healthy controls	tTG positive	Secondary	USA	Sharshiner *et al.*[419]

continued

TABLE 46 Study characteristic: subfertility or recurrent pregnancy loss (*continued*)

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Infertility	400	100	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Tiboni *et al.*[420]
Adults	Case–control (DI)	Infertility	297	100	Healthy controls	tTG positive	Unclear	Islamic Republic of Iran	Zahmatkeshan[421]
Adults	Case–control (DI)	Infertility	1675	26–50	Healthy controls	Double positive for two antibodies	Secondary	Czechia	Vanciková *et al.*[401]
Adults	Cohort	Spontaneous abortion	5060	100	Women without spontaneous abortion	Double positive for two antibodies	Secondary	Italy	Greco *et al.*[310]
Adults	Nested case–control (CD)	Infertility	800	51–75	People without infertility	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Previous abortion	619	100	People without previous abortion	Double positive for two antibodies	Community	USA	Celdir *et al.*[422]
Adults	Nested case–control (DI)	Previous miscarriage	218	100	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Martinelli *et al.*[423]

DI, diagnostic indicator.

TABLE 47 Study characteristic: type 1 diabetes

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Type 1 diabetes	600	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Egypt	Mohammed *et al.*[424]
Adults	Case–control (DI)	Type 1 diabetes	177	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Picarelli *et al.*[425]
Adults	Case–control (DI)	Type 1 diabetes	130	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Dagdelen *et al.*[426]
Adults	Case–control (DI)	Type 1 diabetes	180	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Güvenç *et al.*[427]
Adults	Case–control (DI)	Type 1 diabetes	1680	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Israel	Hanukoglu *et al.*[428]
Adults	Case–control (DI)	Type 1 diabetes	2200	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	UK	Kurien *et al.*[429]
Adults	Case–control (DI)	Type 1 diabetes	346	NR	Healthy controls	tTG positive	Secondary	India	Shivaprasad *et al.*[430]
Adults	Case–control (DI)	Type 1 diabetes	280	51–75	Healthy controls	tTG positive	Secondary	People's Republic of China	Zhao *et al.*[431]
Adults	Cohort	Type 1 diabetes	527	51–75	People without type 1 diabetes	Double positive for two antibodies	Secondary	Malaysia	Yap *et al.*[276]
Adults	Cohort	Type 1 diabetes	6919	51–75	People without type 1 diabetes	Double positive for two antibodies	Community	Finland	Heikkilä *et al.*[321]
Adults	Nested case–control (CD)	Type 1 diabetes	800	51–75	People without type 1 diabetes	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]

continued

TABLE 47 Study characteristic: type 1 diabetes (*continued*)

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Children	Case–control (DI)	Type 1 diabetes	1750	26–50	Children without type 1 diabetes	Other	Secondary	Egypt	Abu-Zekry *et al.*[432]
Children	Case–control (DI)	Type 1 diabetes	971	26–50	Healthy controls	Double positive for two antibodies	Community	Sweden	Adlercreutz *et al.*[433]
Children	Case–control (DI)	Type 1 diabetes	1363	26–50	Healthy controls	Double positive for two antibodies	Community	Denmark	Adlercreutz *et al.*[433]
Children	Case–control (DI)	Type 1 diabetes	335	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	USA	Aktay *et al.*[434]
Children	Case–control (DI)	Type 1 diabetes	209	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Brazil	Baptista *et al.*[435]
Children	Case–control (DI)	Type 1 diabetes	246	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Serbia	Djurić *et al.*[436]
Children	Case–control (DI)	Type 1 diabetes	394	NR	Healthy controls	tTG positive	Unclear	USA	Frohnert *et al.*[437]
Children	Case–control (DI)	Type 1 diabetes	272	26–50	Healthy controls	tTG positive	Secondary	Romania	Gurau *et al.*[438]
Children	Case–control (DI)	Type 1 diabetes	265	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Sweden	Hansson *et al.*[439]
Children	Case–control (DI)	Type 1 diabetes	197	NR	Healthy controls	tTG positive	Secondary	Colombia	Krause *et al.*[440]
Children	Case–control (DI)	Type 1 diabetes	74	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Soyucen *et al.*[441]

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Children	Case–control (DI)	Type 1 diabetes	446	51–75	Healthy controls	tTG positive	Secondary	Colombia	Velasco *et al.*[442]
Mixed	Case–control (DI)	Type 1 diabetes	4491	26–50	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Not *et al.*[443]
Mixed	Case–control (DI)	Type 1 diabetes	219	26–50	Healthy controls	tTG positive	Secondary	Democratic Socialist Republic of Sri Lanka	Premawardhana *et al.*[444]
Mixed	Case–control (DI)	Type 1 diabetes	347	51–75	Healthy controls	tTG positive	Secondary	Germany	Jaeger *et al.*[445]
Mixed	Case–control (DI)	Type 1 diabetes	196	NR	Healthy controls	tTG positive	Secondary	India	Kanungo *et al.*[446]
Mixed	Case–control (DI)	Type 1 diabetes	151	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Sari *et al.*[447]
Mixed	Case–control (DI)	Type 1 diabetes	500	26–50	Healthy controls	tTG positive	Secondary	Italy	Lampasona *et al.*[448]
Mixed	Case–control (DI)	Type 1 diabetes	250	51–75	Healthy controls	tTG positive	Secondary	Islamic Republic of Iran	Sharifi *et al.*[449]
Mixed	Case–control (DI)	Type 1 diabetes	120	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	Islamic Republic of Iran	Sheikholeslami *et al.*[450]

DI, diagnostic indicator; NR, not reported.

TABLE 48 Study characteristic: type 2 diabetes

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Type 2 diabetes	250	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Kizilgul *et al.*[451]
Adults	Case–control (DI)	Type 2 diabetes	113	51–75	Healthy controls	tTG positive	Secondary	Poland	Szepietowska *et al.*[452]
Adults	Case–control (DI)	Type 2 diabetes	247	51–75	Healthy controls	tTG positive	Secondary	People's Republic of China	Zhao *et al.*[431]
Adults	Cohort	Type 2 diabetes	6919	51–75	People without diabetes	Double positive for two antibodies	Community	Finland	Heikkilä *et al.*[321]
Mixed	Case–control (DI)	Type 2 diabetes	338	NR	Healthy controls	tTG positive	Secondary	India	Kanungo *et al.*[446]
Mixed	Case–control (DI)	Type 2 diabetes	332	26–50	Healthy controls	tTG positive	Secondary	Italy	Lampasona *et al.*[448]

DI, diagnostic indicator; NR, not reported.

TABLE 49 Study characteristic: thyroid disease

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Case–control (DI)	Thyroid autoimmunity	1337	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Ravaglia *et al.*[453]
Adults	Case–control (DI)	Thyroid autoimmunity	814	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Ravaglia *et al.*[453]
Adults	Case–control (DI)	Hashimoto's thyroiditis	82	100	Healthy controls	tTG positive	Secondary	Islamic Republic of Iran	Riseh *et al.*[454]
Adults	Case–control (DI)	Graves' disease	354	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Poland	Miskiewicz *et al.*[455]
Adults	Case–control (DI)	Hashimoto's thyroiditis or Graves' disease	4172	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Berti *et al.*[456]
Adults	Case–control (DI)	Graves' disease	124	NR	Healthy controls	EMA positive	Secondary	Ireland	Feighery *et al.*[316]
Adults	Case–control (DI)	Graves' disease	226	76–100	Healthy controls	Double positive for two antibodies	Secondary	UK	Ch'ng *et al.*[457]
Adults	Case–control (DI)	Thyroid autoimmunity	255	76–100	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Guliter *et al.*[458]
Adults	Case–control (DI)	Hashimoto's thyroiditis	470	NR	Healthy controls	Serology and only positive patients biopsied	Secondary	Italy	Volta *et al.*[459]
Adults	Case–control (DI)	Autoimmune and non-autoimmune thyroid disease	318	51–75	Healthy controls	tTG positive	Secondary	People's Republic of China	Zhao *et al.*[431]
Adults	Cohort	Thyroid disorder	1197	26–50	People without thyroid disorder	Double positive for two antibodies	Community	The United Arab Emirates	Abu-Zeid *et al.*[277]

continued

TABLE 49 Study characteristic: thyroid disease (*continued*)

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Thyroid disorder	527	51–75	People without thyroid disorder	Double positive for two antibodies	Secondary	Malaysia	Yap *et al.*[276]
Adults	Cohort	Thyroid disorder	4633	26–50	Healthy controls	tTG positive	Community	Germany	Metzger *et al.*[460]
Adults	Cohort	Thyroid disorder	7339	51–75	People without thyroid disease	EMA positive	Primary	UK	West *et al.*[359]
Adults	Nested case–control (CD)	Thyroiditis, hypo- or hyperthyroidism	800	51–75	People without thyroid disease	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (DI)	TPOAbs	682	NR	Healthy controls	tTG positive	Community	India	Marwaha *et al.*[461]
Children	Case–control (DI)	Thyroid autoimmunity	132	51–75	Healthy controls	Serology and only positive patients biopsied	Unclear	Türkiye	Sahin *et al.*[462]
Children	Case–control (DI)	Thyroid autoimmunity	204	51–75	Healthy controls	Serology and only positive patients biopsied	Secondary	Türkiye	Sari *et al.*[463]
Children	Case–control (DI)	Thyroid autoimmunity	134	NR	Healthy controls	Serology and only positive patients biopsied	NR	Romania	Oana *et al.*[387]
Children	Nested case control (based on CD)	TPOAbs	2030	26–50	Healthy controls	Serology and only positive patients biopsied	Community	Sweden	van der Pals *et al.*[464]
Children	Nested case–control (DI)	TPOAbs	472	NR	Healthy controls	tTG positive	Community	India	Marwaha *et al.*[461]
Mixed	Case–control (DI)	Free T_4 or TSH	77	51–75	Healthy controls	Double positive for two antibodies	Secondary	Iraq	Risan[465]
Mixed	Case–control (DI)	Thyroid autoimmunity	652	76–100	Healthy controls	tTG positive	Community	Brazil	de Melo *et al.*[466]

DI, diagnostic indicator; NR, not reported; T_4, thyroxine; TPOAbs, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

TABLE 50 Study characteristic: vomiting and nausea

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Vomiting	2843	NR	People without vomiting	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Cohort	Nausea	3847	51–75	People without nausea	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Adults	Cohort	Vomiting	3847	51–75	People without vomiting	Double positive for two antibodies	Community	USA	Katz *et al.*[296]
Children	Cohort	Vomiting	4327	NR	Children without vomiting	Double positive for two antibodies	Community	UK	Bingley *et al.*[2]
Children	Cohort	Vomiting	18,593	51–75	Children without vomiting	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Nausea	1562	26–50	Children without nausea (after eating)	tTG positive	Community	The Netherlands	Jansen *et al.*[182]
Children	Cohort	Vomiting	9918	51–75	Children without vomiting	tTG positive	Secondary	USA	Stahl *et al.*[293]

NR, not reported.

TABLE 51 Study characteristic: weight loss

Population group	Study design	Indicator details	Sample size (*n*)	Sex (% female)	Control group	Reference standard	Care setting	Location	Reference
Adults	Cohort	Weight loss	1960	NR	People without weight loss	Double positive for two antibodies	Community	USA	Choung *et al.*[288]
Adults	Nested case–control (CD)	Weight loss	800	51–75	People without unexplained weight loss	Double positive for two antibodies	Primary and secondary	USA	Hujoel *et al.*[290]
Adults	Nested case–control (CD)	Weight loss	381	51–75	People without weight loss	Double positive for two antibodies	Secondary	USA	Godfrey *et al.*[236]
Children	Cohort	Weight loss	18,680	51–75	Children without weight loss	Serology and only positive patients biopsied	Community	Türkiye	Dalgic *et al.*[292]
Children	Cohort	Weight loss	9918	51–75	Children without weight loss	tTG positive	Secondary	USA	Stahl *et al.*[293]

NR, not reported.

Appendix 5 Risk of bias

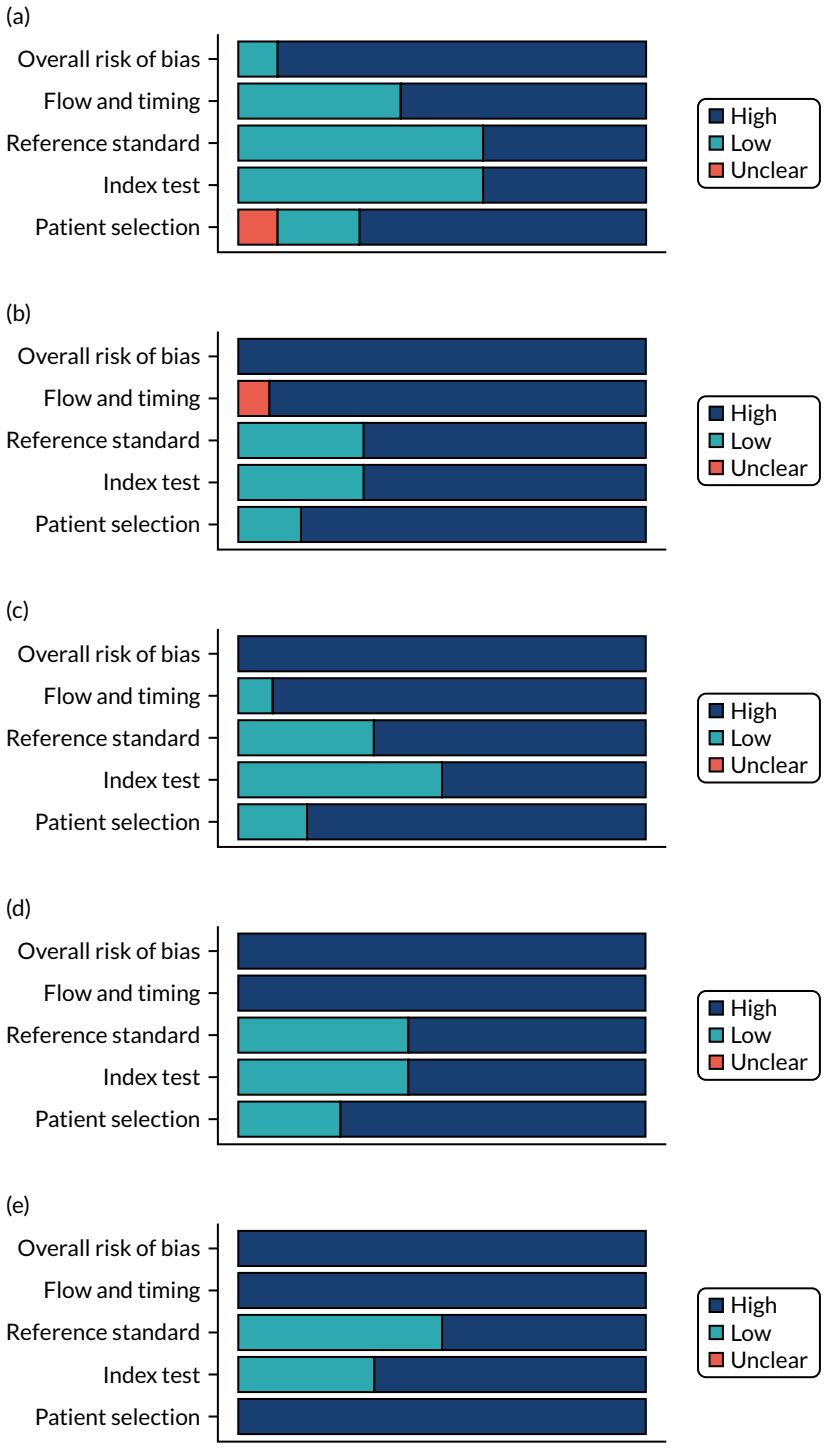

FIGURE 27 Summary graphs of risk of bias. (a) Symptom: acid reflux symptoms; (b) symptom: diarrhoea; (c) symptom: abdominal pain; (d) symptom: constipation; (e) symptom: bloating and abdominal distension; (f) symptom: vomiting and nausea; (g) symptom: weight loss; (h) risk condition: type 1 diabetes; (i) risk condition: thyroid disease; (j) risk condition: anaemia; (k) risk condition: IBS; (l) risk condition: chronic liver disease; (m) risk condition: arthritis; (n) risk condition: subfertility and pregnancy loss; (o) risk condition: epilepsy; (p) risk condition: osteoporosis; (q) risk condition: fracture; (r) risk condition: inflammatory bowel disease; (s) risk condition: systemic lupus erythematosus; (t) risk condition: type 2 diabetes; (u) risk condition: dermatitis herpetiformis; (v) risk condition: migraine; (w) risk condition: multiple sclerosis; (x) risk condition: psoriasis; and (y) family history of CD. Note that each of the bars represents 100% of the studies per indicator. (*continued*)

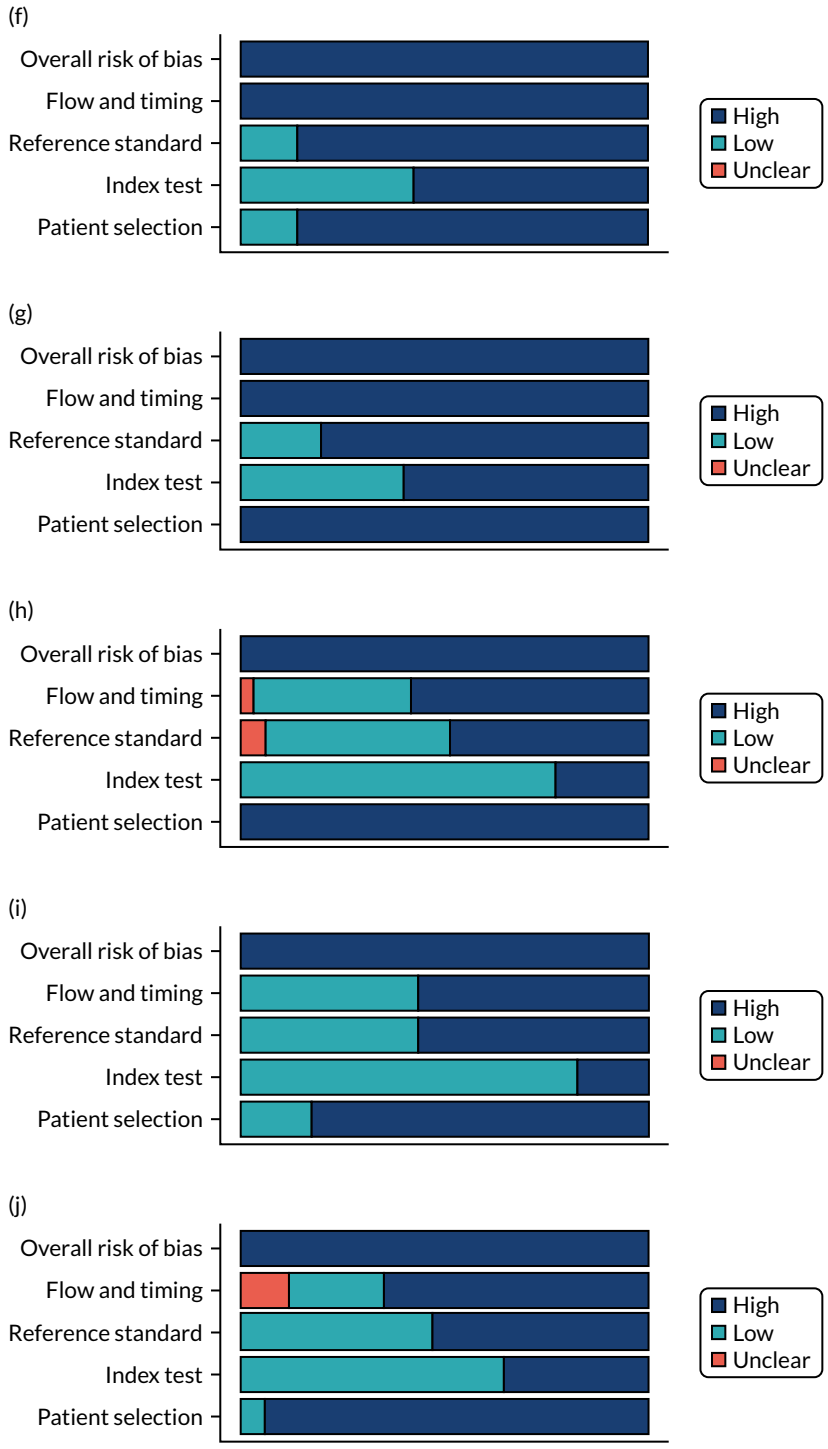

FIGURE 27 Summary graphs of risk of bias. (a) Symptom: acid reflux symptoms; (b) symptom: diarrhoea; (c) symptom: abdominal pain; (d) symptom: constipation; (e) symptom: bloating and abdominal distension; (f) symptom: vomiting and nausea; (g) symptom: weight loss; (h) risk condition: type 1 diabetes; (i) risk condition: thyroid disease; (j) risk condition: anaemia; (k) risk condition: IBS; (l) risk condition: chronic liver disease; (m) risk condition: arthritis; (n) risk condition: subfertility and pregnancy loss; (o) risk condition: epilepsy; (p) risk condition: osteoporosis; (q) risk condition: fracture; (r) risk condition: inflammatory bowel disease; (s) risk condition: systemic lupus erythematosus; (t) risk condition: type 2 diabetes; (u) risk condition: dermatitis herpetiformis; (v) risk condition: migraine; (w) risk condition: multiple sclerosis; (x) risk condition: psoriasis; and (y) family history of CD. Note that each of the bars represents 100% of the studies per indicator. (*continued*)

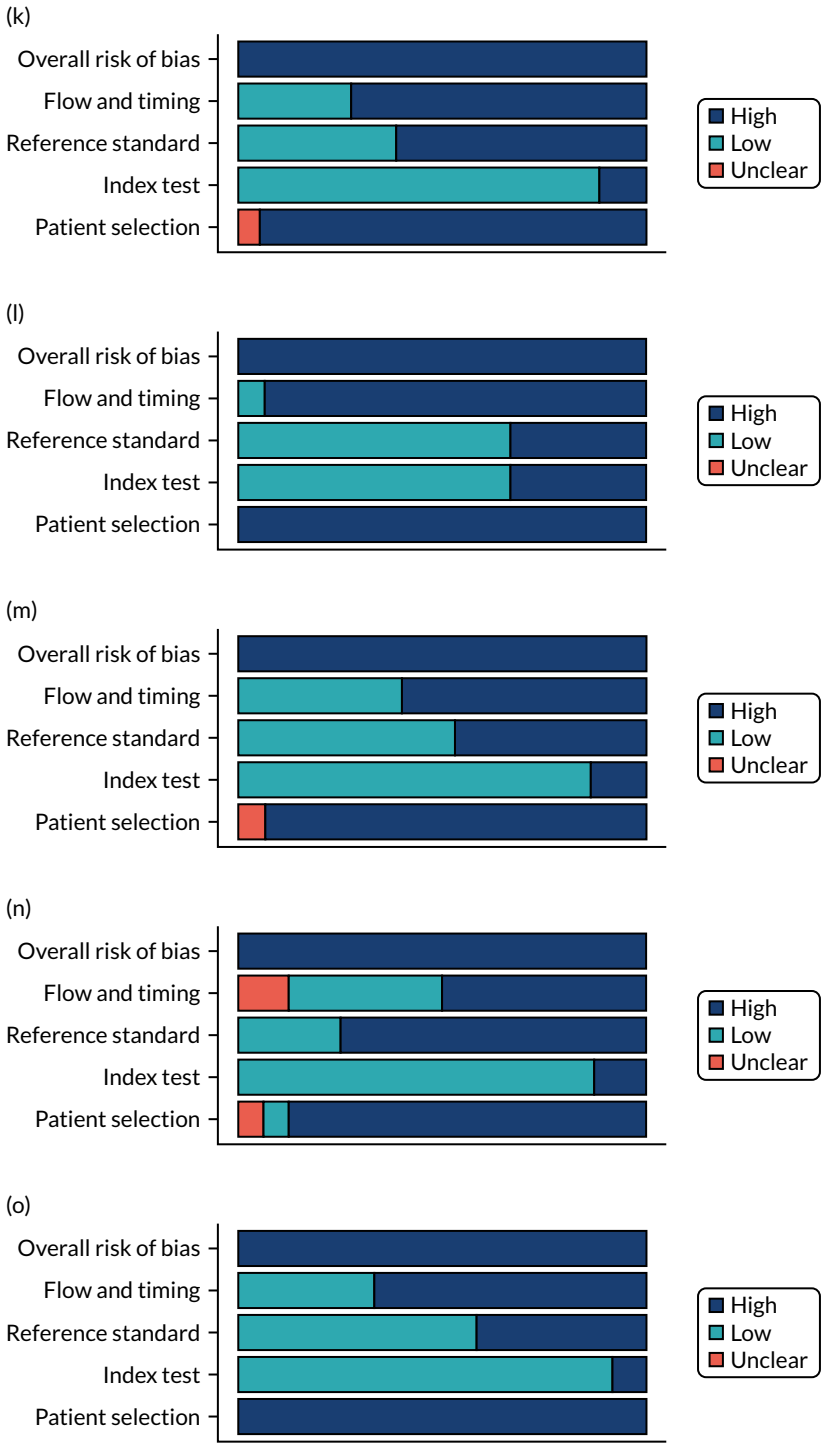

FIGURE 27 Summary graphs of risk of bias. (a) Symptom: acid reflux symptoms; (b) symptom: diarrhoea; (c) symptom: abdominal pain; (d) symptom: constipation; (e) symptom: bloating and abdominal distension; (f) symptom: vomiting and nausea; (g) symptom: weight loss; (h) risk condition: type 1 diabetes; (i) risk condition: thyroid disease; (j) risk condition: anaemia; (k) risk condition: IBS; (l) risk condition: chronic liver disease; (m) risk condition: arthritis; (n) risk condition: subfertility and pregnancy loss; (o) risk condition: epilepsy; (p) risk condition: osteoporosis; (q) risk condition: fracture; (r) risk condition: inflammatory bowel disease; (s) risk condition: systemic lupus erythematosus; (t) risk condition: type 2 diabetes; (u) risk condition: dermatitis herpetiformis; (v) risk condition: migraine; (w) risk condition: multiple sclerosis; (x) risk condition: psoriasis; and (y) family history of CD. Note that each of the bars represents 100% of the studies per indicator. (*continued*)

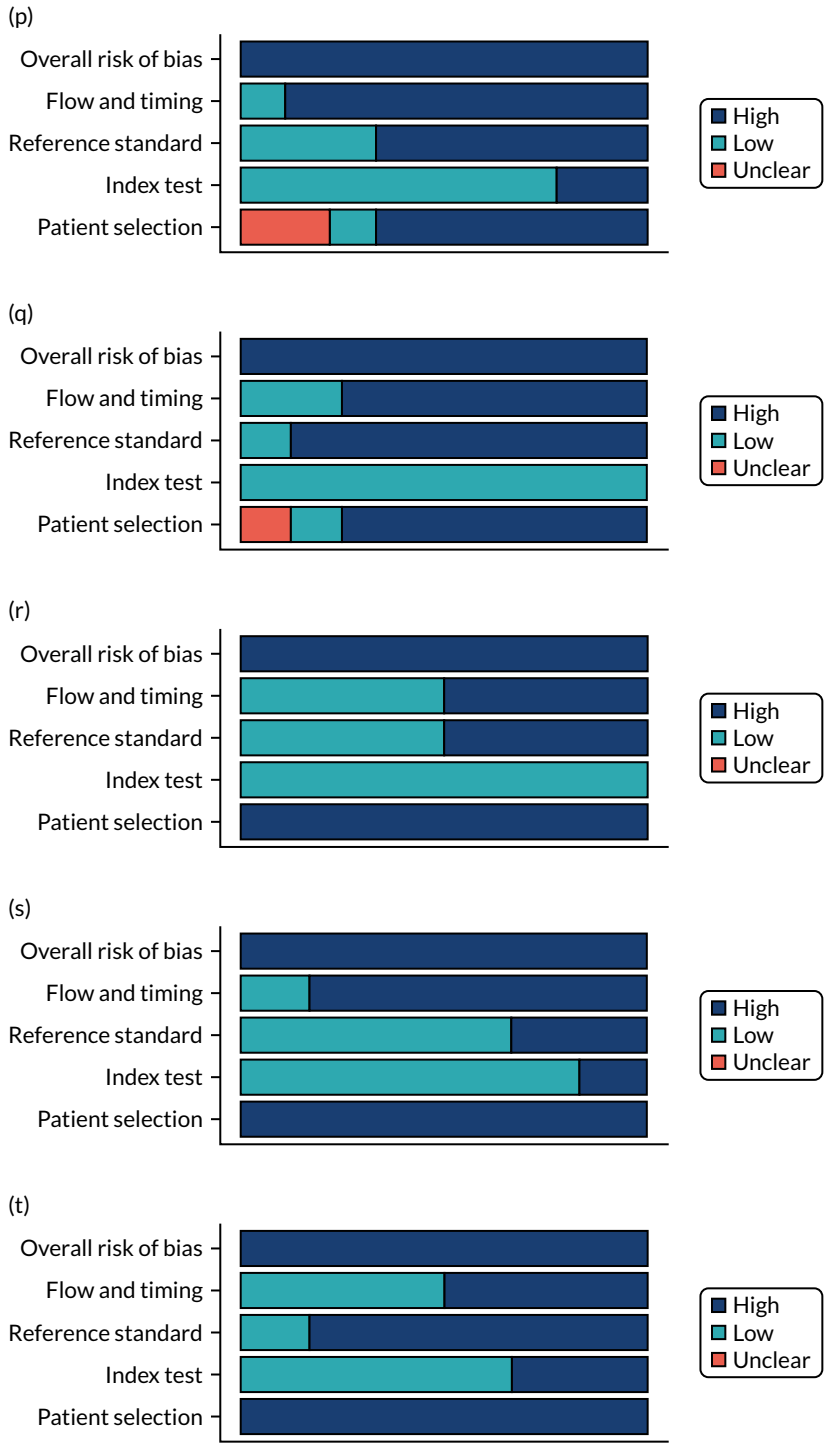

FIGURE 27 Summary graphs of risk of bias. (a) Symptom: acid reflux symptoms; (b) symptom: diarrhoea; (c) symptom: abdominal pain; (d) symptom: constipation; (e) symptom: bloating and abdominal distension; (f) symptom: vomiting and nausea; (g) symptom: weight loss; (h) risk condition: type 1 diabetes; (i) risk condition: thyroid disease; (j) risk condition: anaemia; (k) risk condition: IBS; (l) risk condition: chronic liver disease; (m) risk condition: arthritis; (n) risk condition: subfertility and pregnancy loss; (o) risk condition: epilepsy; (p) risk condition: osteoporosis; (q) risk condition: fracture; (r) risk condition: inflammatory bowel disease; (s) risk condition: systemic lupus erythematosus; (t) risk condition: type 2 diabetes; (u) risk condition: dermatitis herpetiformis; (v) risk condition: migraine; (w) risk condition: multiple sclerosis; (x) risk condition: psoriasis; and (y) family history of CD. Note that each of the bars represents 100% of the studies per indicator. (*continued*)

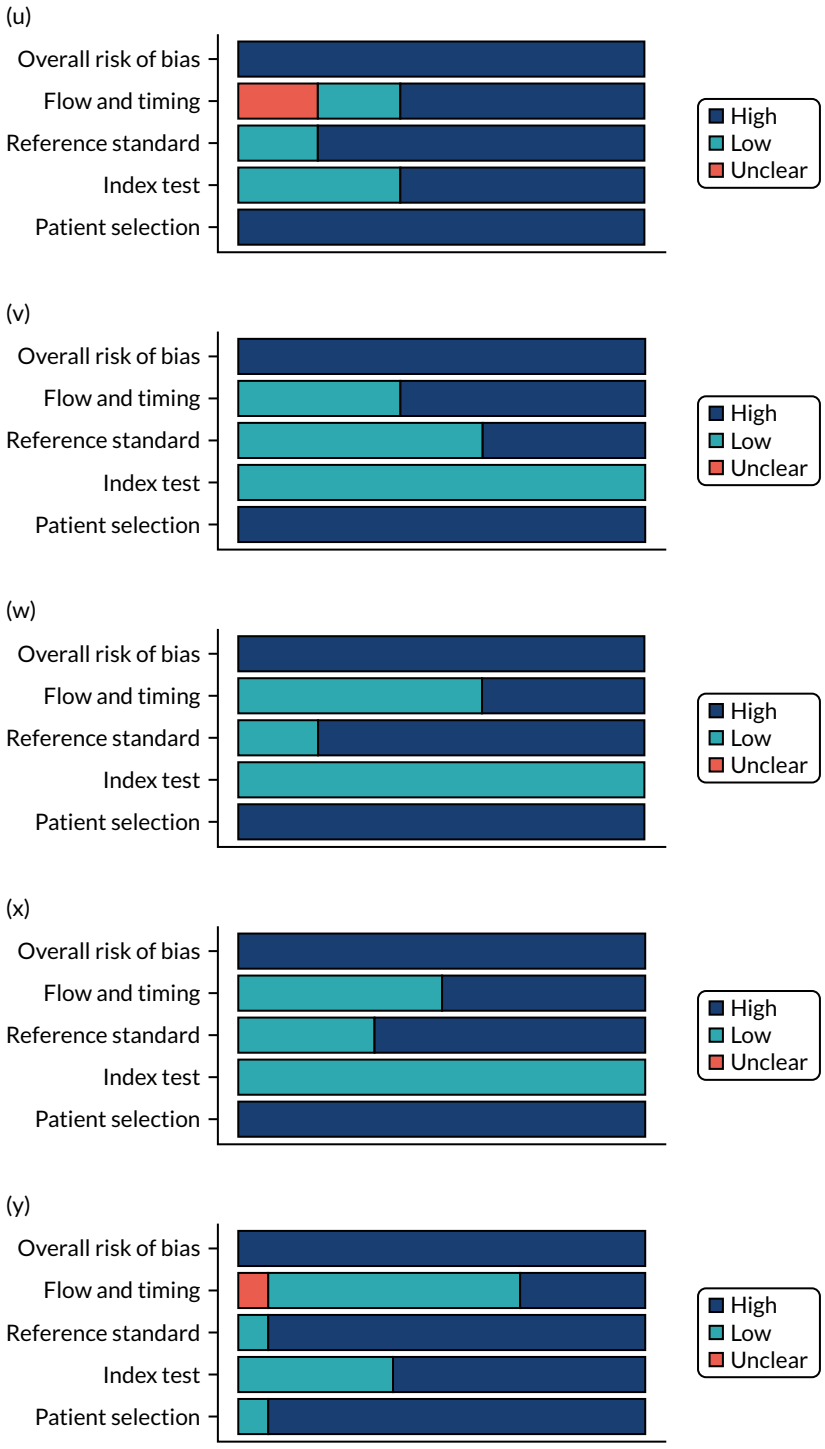

FIGURE 27 Summary graphs of risk of bias. (a) Symptom: acid reflux symptoms; (b) symptom: diarrhoea; (c) symptom: abdominal pain; (d) symptom: constipation; (e) symptom: bloating and abdominal distension; (f) symptom: vomiting and nausea; (g) symptom: weight loss; (h) risk condition: type 1 diabetes; (i) risk condition: thyroid disease; (j) risk condition: anaemia; (k) risk condition: IBS; (l) risk condition: chronic liver disease; (m) risk condition: arthritis; (n) risk condition: subfertility and pregnancy loss; (o) risk condition: epilepsy; (p) risk condition: osteoporosis; (q) risk condition: fracture; (r) risk condition: inflammatory bowel disease; (s) risk condition: systemic lupus erythematosus; (t) risk condition: type 2 diabetes; (u) risk condition: dermatitis herpetiformis; (v) risk condition: migraine; (w) risk condition: multiple sclerosis; (x) risk condition: psoriasis; and (y) family history of CD. Note that each of the bars represents 100% of the studies per indicator.

Appendix 6 Forest plots of sensitivity and specificity per diagnostic indicator

Symptoms

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Bingley *et al.*[2]	Any stomach pains	28	2557	14	1728
Choung *et al.*[287]	Abdominal pain	6	803	25	2362
Dalgic *et al.*[291]	Abdominal pain	39	6303	52	12,278
Fitzpatrick *et al.*[290]	Recurrent abdominal pain	1	91	1	80
Godfrey *et al.*[234]	Abdominal pain	46	92	81	162
Hopper *et al.*[285]	Acute abdominal pain	10	290	2	298
Hujoel *et al.*[289]	Recurrent abdominal pain	29	34	371	366
Jansen *et al.*[182]	Abdominal pain	24	1227	21	1821
Stahl *et al.*[292]	Stomach aches	50	2142	137	7589
Oliveira *et al.*[288]	Abdominal pain	6	32	8	2930
Sanders *et al.*[286]	Acute abdominal pain	10	290	2	298
Wahab *et al.*[180]	Abdominal pain	6	484	45	3180
Summary					

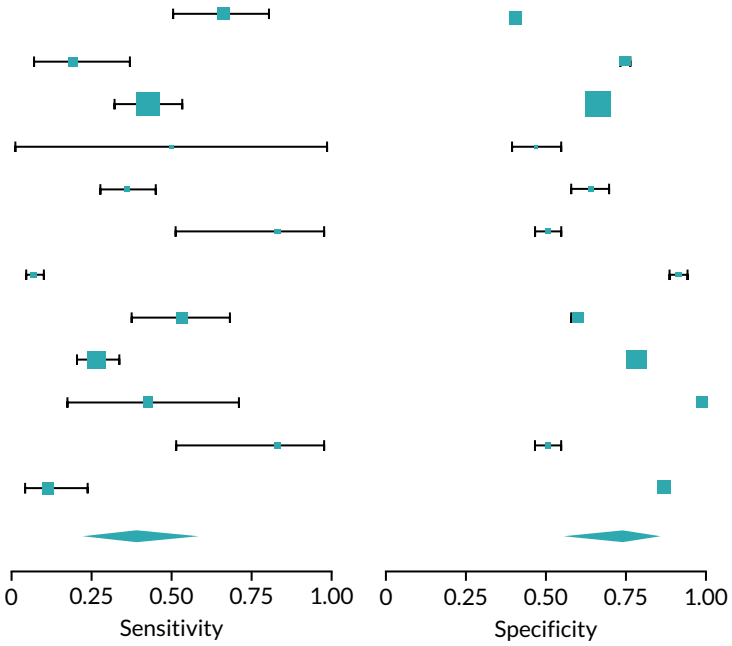

FIGURE 28 Abdominal pain. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Choung *et al.*[288]	Dyspepsia	2	149	27	2940
Hujoel *et al.*[290]	Dyspepsia	8	19	392	381
Katz *et al.*[296]	Heartburn	12	1463	19	2353
Lara-Carmona *et al.*[297]	Dyspepsia	1	86	4	336
Lasa *et al.*[294]	Dyspepsia	4	316	2	318
Lecleire *et al.*[295]	Dyspepsia	1	79	0	25
Locke *et al.*[300]	Dyspepsia	2	32	2	76
Ludvigsson *et al.*[299]	Gastro-oesophageal reflux symptoms	8	392	10	590
Tikkakoski *et al.*[298]	Heartburn	13	544	23	1306
Vivas *et al.*[301]	Functional dyspepsia	3	89	1	164
Summary					

FIGURE 29 Acid reflux symptoms. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Choung *et al.*[288]	Bloating	1	412	21	1396
Dalgic *et al.*[292]	Abdominal distension	10	1825	80	16,683
Hujoel *et al.*[290]	Bloating	8	4	392	396
Katz *et al.*[296]	Bloating	9	1305	22	2511
Nenna *et al.*[329]	Abdominal distension	17	1394	28	4294
Tikkakoski *et al.*[298]	Bloating	19	869	17	981
Summary					

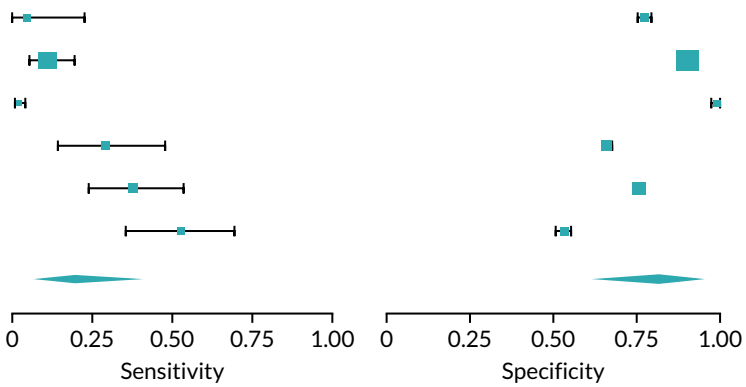

FIGURE 30 Bloating or abdominal distension. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Fifi *et al.*[331]	Functional constipation	1	202	3	416
Bingley *et al.*[2]	Constipation	6	435	36	3850
Çakir *et al.*[330]	Chronic constipation	5	308	6	984
Choung *et al.*[288]	Constipation	4	270	27	2895
Dalgic *et al.*[292]	Constipation	13	2035	77	16,451
Hujoel *et al.*[290]	Constipation	13	16	387	384
Jansen *et al.*[182]	Constipation	6	572	40	2502
Katz *et al.*[296]	Constipation	11	1114	20	2702
Stahl *et al.*[293]	Constipation	22	1158	165	8573
Oliveira *et al.*[289]	Constipation	5	83	9	2879
Tikkakoski *et al.*[298]	Constipation	9	322	27	1528
Wahab *et al.*[180]	Constipation	6	702	45	2962
Summary					

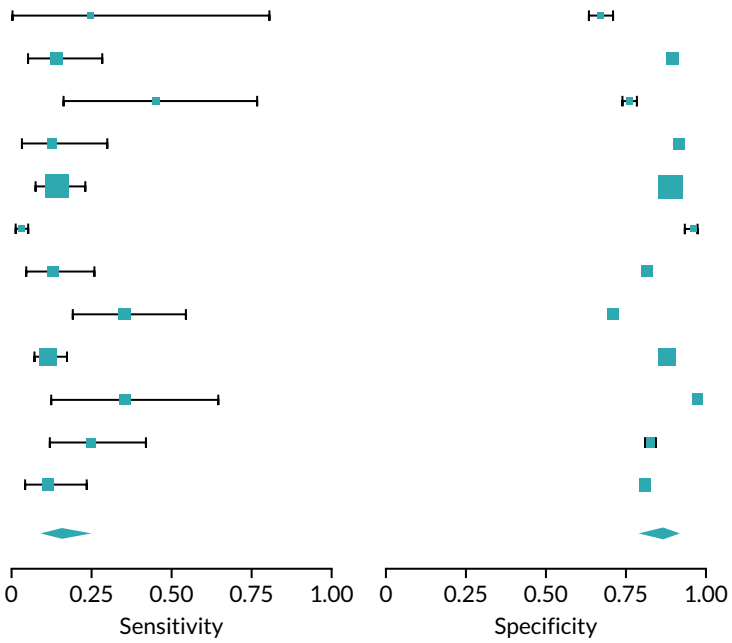

FIGURE 31 Constipation. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abu-Zeid *et al.*[277]	Diarrhoea	0	5	14	1178
Bingley *et al.*[2]	Diarrhoea	21	1450	21	2835
Choung *et al.*[288]	Diarrhoea	1	283	30	2872
Dalgic *et al.*[291]	Diarrhoea	7	1545	83	16,967
Godfrey *et al.*[236]	Diarrhoea	27	65	100	189
Hujoel *et al.*[290]	Diarrhoea	13	24	387	376
Imanzadeh *et al.*[335]	Diarrhoea	54	771	5	820
Jansen *et al.*[182]	Diarrhoea	2	90	42	2881
Katz *et al.*[296]	Diarrhoea	5	964	26	2852
Stahl *et al.*[293]	Diarrhoea	11	454	176	9277
Oliveira *et al.*[289]	Diarrhoea	4	31	10	2931
Tikkakoski *et al.*[298]	Diarrhoea	14	588	22	1262
Wahab *et al.*[180]	Diarrhoea	2	114	49	3550
Summary					

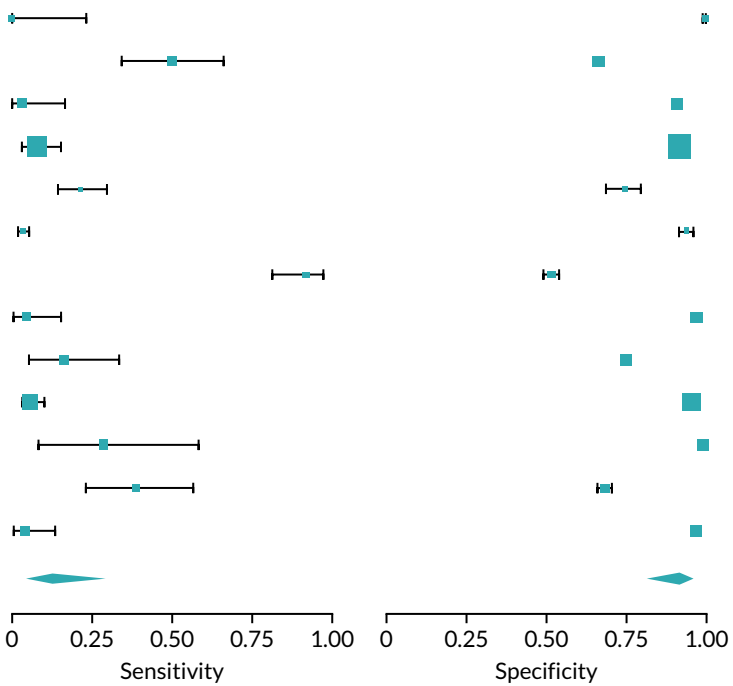

FIGURE 32 Diarrhoea. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

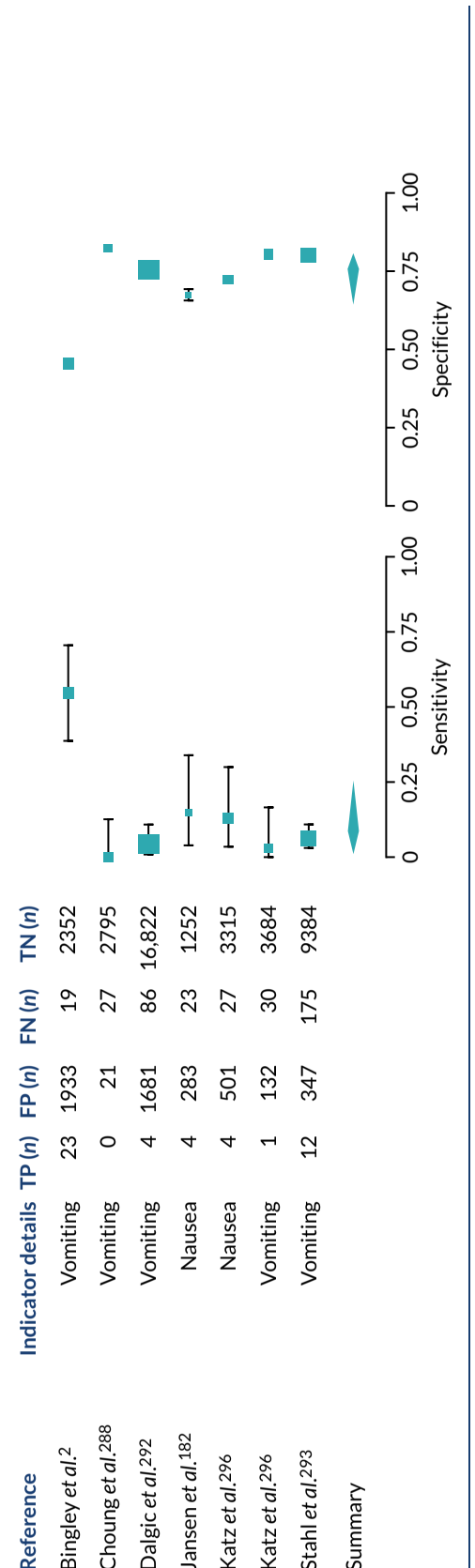

FIGURE 33 Vomiting and nausea. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Risk conditions

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abu-Zeid *et al.*[277]	Anaemia	5	86	9	1097
Alexander *et al.*[302]	Low haemoglobin levels	9	77	3	85
Cikrikcioglu *et al.*[306]	IDA	2	16	0	79
Ertekin *et al.*[314]	IDA	4	126	7	1126
Godfrey *et al.*[236]	Anaemia	23	33	104	221
Greco *et al.*[310]	Anaemia	22	564	41	4433
Hujoel *et al.*[290]	Anaemia	24	24	376	376
Javid *et al.*[303]	IDA of obscure origin	13	148	2	158
Kalayci *et al.*[311]	IDA	6	129	0	223
Lasa *et al.*[305]	IDA	15	120	2	131
Morawiec-Szymonik *et al.*[307]	Pernicious anaemia	4	120	1	40
Narang *et al.*[313]	IDA	6	146	0	152
Ransford *et al.*[308]	Anaemia	11	473	1	497
Sanders *et al.*[309]	IDA	3	61	9	1127
Shahriari *et al.*[312]	IDA	0	137	0	47
Uçardağ *et al.*[304]	IDA of obscure origin	6	71	1	118
Yap *et al.*[276]	Anaemia/IDA	0	15	6	506
Summary					

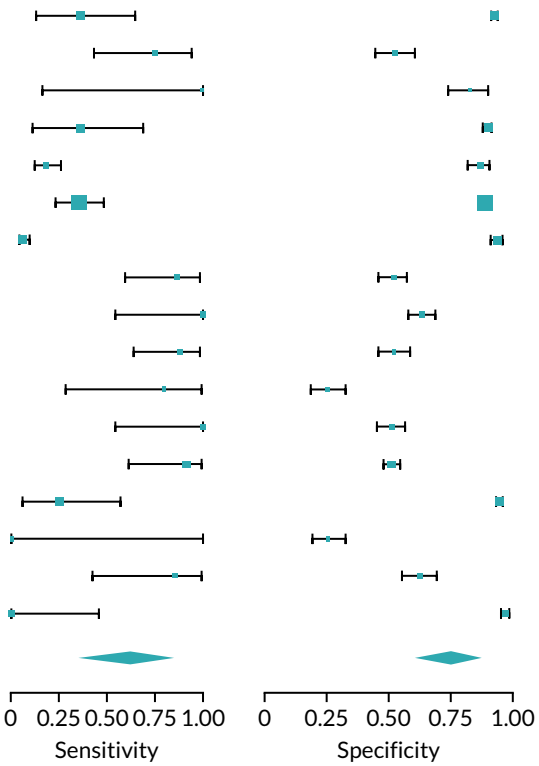

FIGURE 34 Anaemia. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Bizzaro *et al.*[315]	RA	0	100	0	120
Feighery *et al.*[316]	RA	1	52	0	30
Gheita *et al.*[322]	Juvenile rheumatic diseases	32	28	6	24
Heikkilä *et al.*[321]	RA	3	128	66	6722
Hujoel *et al.*[290]	RA	5	3	395	397
Luft *et al.*[320]	RA	0	50	1	49
Nisihara *et al.*[317]	RA	0	85	0	97
Picarelli *et al.*[318]	Arthritis (PsA, RA or AS)	0	183	0	54
Riente *et al.*[319]	Arthritis (PsA, RA or AS)	3	194	3	75
Robazzi *et al.*[326]	Juvenile idiopathic arthritis	1	52	0	17
Sahin *et al.*[323]	Juvenile idiopathic arthritis	0	96	0	85
Skrabl-Baumgartner *et al.*[324]	Juvenile idiopathic arthritis	4	91	0	110
Stagi *et al.*[325]	Juvenile idiopathic arthritis	10	141	1	157
Taneja *et al.*[327]	Juvenile idiopathic arthritis	7	813	3	202
Toğrol *et al.*[328]	AS	1	29	0	19
Summary					

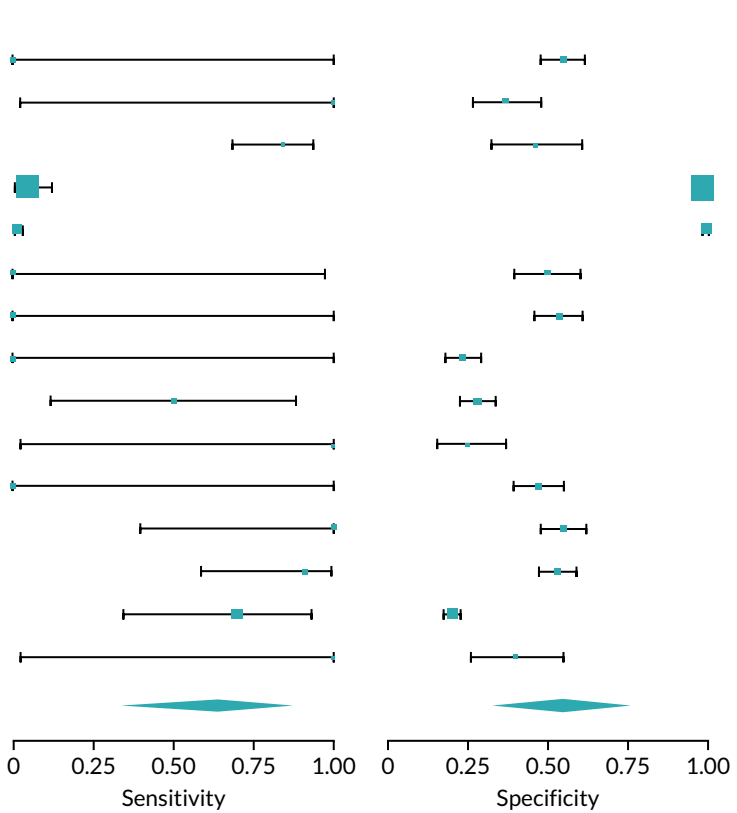

FIGURE 35 Arthritis. AS, ankylosing spondylitis; FN, false negative; FP, false positive; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Godfrey *et al.*[236]	Dermatitis herpetiformis	5	0	122	254
Hujoel *et al.*[290]	Dermatitis herpetiformis	7	0	393	400
Kumar *et al.*[332]	Dermatitis herpetiformis	32	12	0	106
Smecuol *et al.*[334]	Dermatitis herpetiformis	9	9	0	34
Velikova *et al.*[333]	Dermatitis herpetiformis	11	15	0	20
Summary					

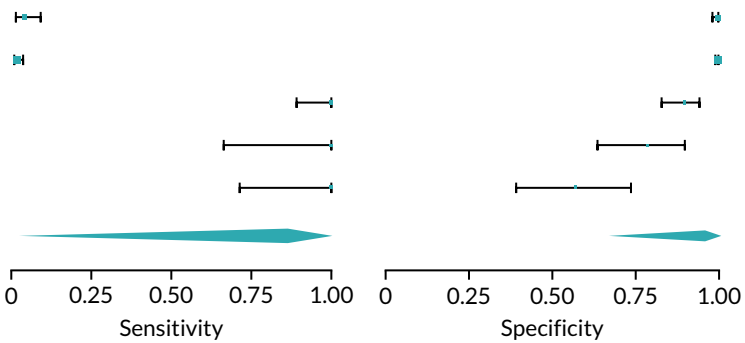

FIGURE 36 Dermatitis herpetiformis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Mavroudi *et al.*[337]	Epilepsy	5	250	0	280
Dai *et al.*[339]	Epilepsy	2	88	0	100
Dalgiç *et al*[338]	Epilepsy	2	168	0	103
Djurić *et al.*[340]	Epilepsy	1	124	1	149
Giordano *et al.*[341]	Epilepsy	5	267	3	297
Hujoel *et al.*[290]	Epilepsy/ataxia	2	7	398	393
Işikay *et al.*[342]	Epilepsy	2	212	0	166
Işikay *et al.*[343]	Epilepsy	6	594	0	400
Lahat *et al.*[344]	Epilepsy	0	36	0	34
Mavroudi *et al.*[337]	Epilepsy	5	250	0	280
Pratesi *et al.*[344]	Epilepsy	2	253	15	4390
Ranua *et al.*[336]	Epilepsy	37	816	19	555
Summary					

FIGURE 37 Epilepsy. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Agardh *et al.*[358]	Fracture	15	802	44	5619
Choung *et al.*[360]	Fracture	27	58	254	504
Heikkilä *et al.*[321]	Vertebra fracture	0	51	69	6799
Hjelle *et al.*[355]	Acute distal radius or ankle fracture	11	123	3	91
Hjelle *et al.*[354]	Acute distal radius or ankle fracture	10	390	5	192
LeBoff *et al.*[356]	Hip fracture	3	154	1	50
Potter *et al.*[357]	Non-traumatic fractures	8	149	12	1952
West *et al.*[359]	Fracture of the wrist	7	452	80	6806
Summary					

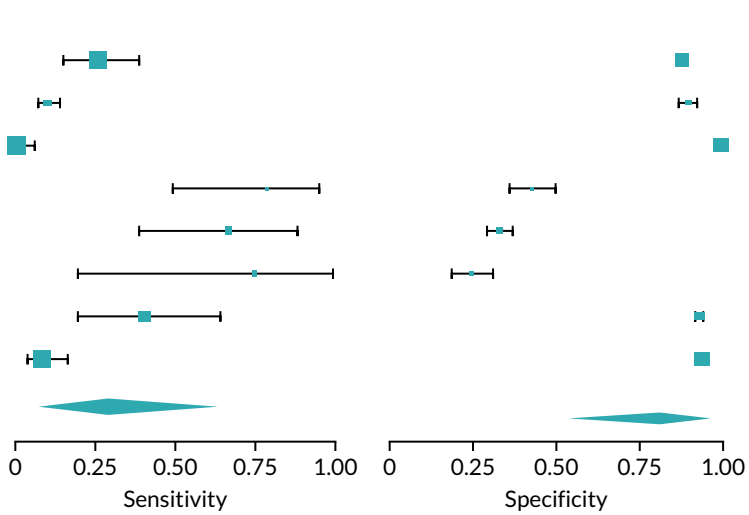

FIGURE 38 Fracture. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Bizzaro *et al.*[315]	Ulcerative colitis or Crohn's disease	1	169	0	120
El-Matary *et al.*[366]	Ulcerative colitis or Crohn's disease	1	163	1	163
Horoldt *et al.*[363]	Ulcerative colitis or Crohn's disease	1	273	5	586
Kull *et al.*[367]	Ulcerative colitis	0	49	0	37
Leeds *et al.*[364]	Ulcerative colitis or Crohn's disease	3	351	5	596
Watanabe *et al.*[365]	Ulcerative colitis or Crohn's disease	14	158	1	189
Summary					

FIGURE 39 Inflammatory bowel disease. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Khayyat[393]	IBS	21	284	3	201
Almazar *et al.*[370]	IBS	6	527	3	528
Cash *et al.*[371]	IBS	2	490	2	456
Choung *et al.*[288]	IBS	1	433	30	2732
Domżał-Magrowska *et al.*[372]	IBS	5	43	2	18
Godfrey *et al.*[236]	IBS	13	31	114	223
Hujoel *et al.*[290]	IBS	8	18	392	382
Kou *et al.*[373]	IBS	12	234	2	244
Locke *et al.*[300]	IBS	2	48	2	76
Mehdi *et al.*[368]	IBS	0	107	0	126
Olen *et al.*[380]	Functional GI disorder	12	553	111	4592
Respondek *et al.*[369]	IBS	27	123	0	50
Saito-Loftus *et al.*[374]	IBS	6	560	3	552
Sánchez-Vargas *et al.*[375]	IBS	10	390	2	398
Sanders *et al.*[376]	IBS	14	286	2	298
Sanders *et al.*[309]	IBS	4	119	8	1069
Vargas *et al.*[377]	IBS	11	328	3	336
Wang *et al.*[378]	IBS	7	388	2	361
Summary					

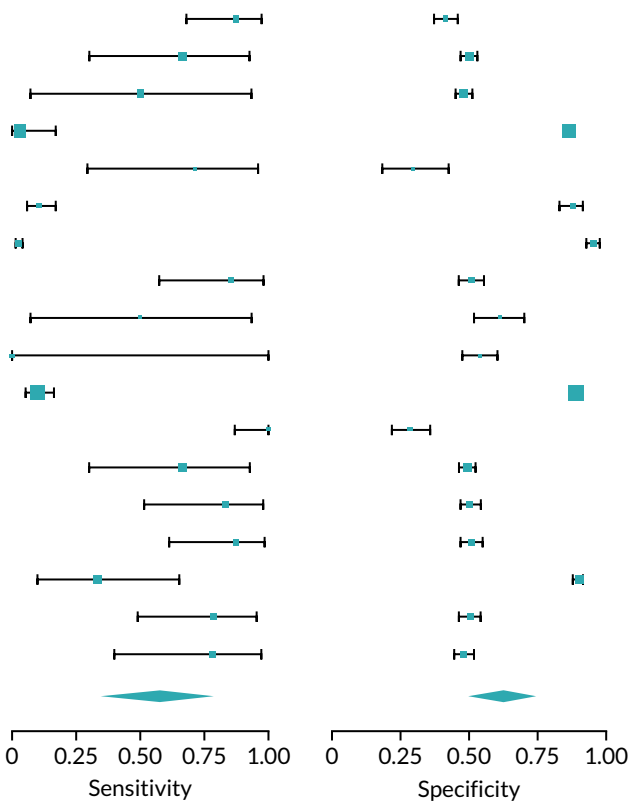

FIGURE 40 IBS. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abu-Zeid *et al.*[277]	Hepatitis	0	11	14	1172
Oana *et al.*[387]	Autoimmune hepatitis	4	58	0	60
Bizzaro *et al.*[315]	Primary biliary cirrhosis	0	48	0	120
Chatzicostas *et al.*[381]	Primary biliary cirrhosis	0	62	0	100
Durante-Mangoni *et al.*[382]	Chronic hepatitis C	7	163	1	224
El-Shabrawi *et al.*[386]	Autoimmune hepatitis	3	23	0	20
Germenis *et al.*[388]	HCV, HBV, AIH, PBC, PSC, NAFLD-ALD, NAFLD and others	3	731	4	1346
Hernandez *et al.*[383]	Chronic hepatitis C	0	195	0	80
Hujoel *et al.*[290]	Unexplained abnormal levels of AST/ALT	16	16	384	384
Sjöberg *et al.*[384]	ALD, HCV, PBC, PSC and CH	2	463	0	1537
Villalta *et al.*[389]	Autoimmune hepatitis	3	44	0	120
Villalta *et al.*[389]	Chronic hepatitis C	0	100	0	120
Vivas *et al.*[301]	Chronic hepatitis C	0	102	1	164
Yap *et al.*[276]	Hepatic diseases	0	3	6	518
Yuan *et al.*[385]	Abnormal liver function tests	0	125	0	125
Summary					

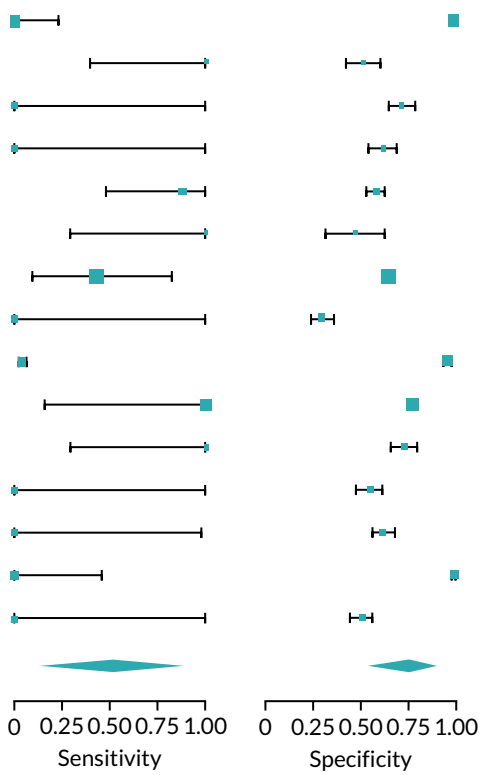

FIGURE 41 Chronic liver disease. ALD, alcoholic liver disease; ALT, alanine transaminase; AST, aspartate transaminase; CH, chronic hepatitis; FN, false negative; FP, false positive; HBV, chronic hepatitis B virus; HCV, chronic hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Alehan *et al.*[391]	Migraine	4	69	1	146
Balci *et al.*[390]	Migraine	0	81	0	176
Gabrielli *et al.*[274]	Migraine	4	86	1	235
Inaloo *et al.*[392]	Migraine	2	98	30	1470
Lahat *et al.*[344]	Migraine headaches	0	41	0	34
Summary					

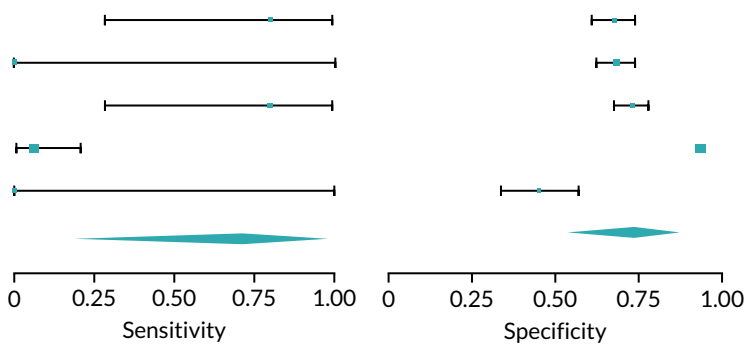

FIGURE 42 Migraine. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abolfazli *et al.*[393]	Multiple sclerosis	0	34	0	34
Khoshbaten *et al.*[397]	Multiple sclerosis	0	100	0	121
Nicoletti *et al.*[394]	Multiple sclerosis	0	217	1	199
Rodrigo *et al.*[395]	Multiple sclerosis	7	65	3	120
Roth *et al.*[396]	Multiple sclerosis	0	85	1	99
Summary					

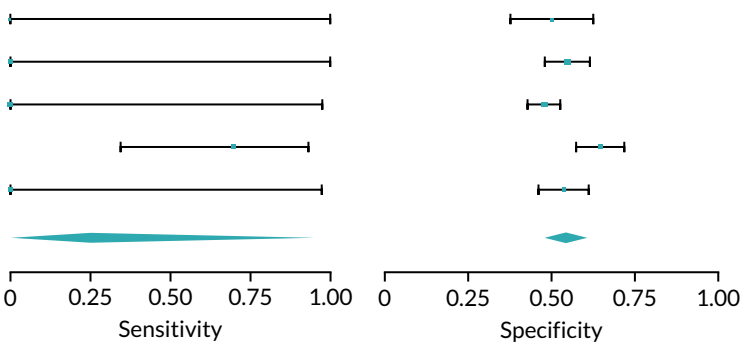

FIGURE 43 Multiple sclerosis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Agardh *et al.*[358]	Osteoporosis	8	417	51	6004
Choung *et al.*[360]	Osteoporosis	1	2	280	560
Gusso *et al.*[398]	Osteoporosis	1	99	0	97
Hujoel *et al.*[290]	Osteoporosis	4	5	396	395
Potter *et al.*[357]	Osteoporosis	11	60	144	1906
Shahbazkhani *et al.*[399]	Osteoporosis	5	455	1	99
Shen *et al.*[402]	Osteoporosis	4	381	37	6541
Stenson *et al.*[400]	Osteoporosis	9	257	3	571
Vanciková *et al.*[401]	Osteoporosis	1	101	6	1306
Summary					

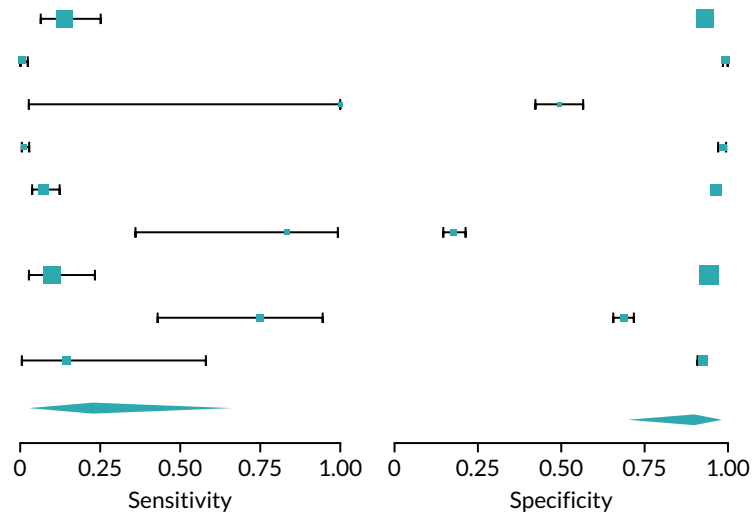

FIGURE 44 Osteoporosis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Akbulut *et al.*[404]	Psoriasis	1	36	0	50
De Bastiani *et al.*[403]	Psoriasis	9	209	1	263
Montesu *et al.*[406]	Psoriasis	2	98	0	100
Dhattarwal *et al.*[405]	Chronic plaque psoriasis	2	78	0	80
Nagui *et al.*[407]	Psoriasis	14	27	9	32
Singh *et al.*[408]	Psoriasis	6	50	0	60
Summary					

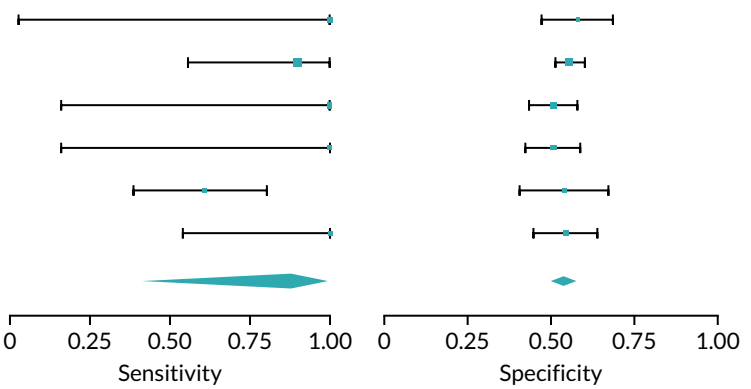

FIGURE 45 Psoriasis. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Bizzaro *et al.*[315]	Systemic lupus erythematosus	1	99	0	120
Feighery *et al.*[316]	Systemic lupus erythematosus	0	46	0	30
Luft *et al.*[320]	Systemic lupus erythematosus	1	49	1	49
Marai *et al.*[409]	Systemic lupus erythematosus	1	99	0	120
Picceli *et al.*[410]	Systemic lupus erythematosus	5	189	0	103
Sahin *et al.*[411]	Systemic lupus erythematosus	0	50	0	41
Summary					

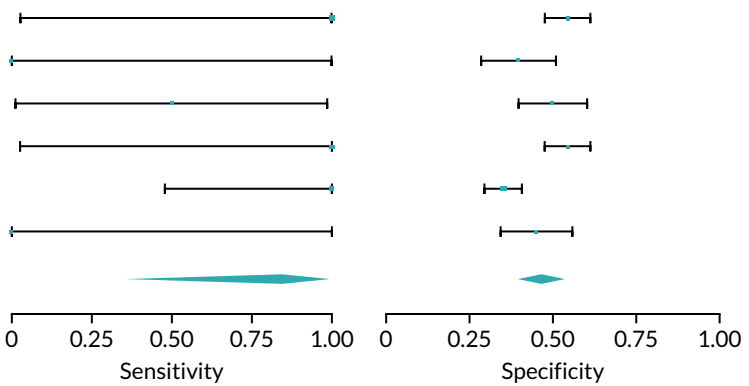

FIGURE 46 Systemic lupus erythematosus. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Cedíková *et al.*[412]	Recurrent miscarriages or implantation failure	13	429	0	86
Greco *et al.*[310]	Spontaneous abortion	8	390	55	4607
Herraiz-Nicuesa *et al.*[412]	Recurrent miscarriages or implantation failure	25	242	0	12
Hujoel *et al.*[290]	Infertility	5	11	395	389
Kumar *et al.*[415]	Unexplained infertility	13	217	4	301
Kumar *et al.*[415]	Recurrent pregnancy loss	7	97	4	301
Kutteh *et al.*[416]	Recurrent pregnancy loss	9	699	1	99
Celdir *et al.*[422]	Previous abortion	68	135	141	275
Martinelli *et al.*[423]	Previous miscarriage	4	45	8	161
Remes-Troche *et al.*[413]	Unexplained infertility or recurrent miscarriages	6	165	1	170
Sarikaya *et al.*[417]	Recurrent pregancy loss	1	44	3	38
Shamaly *et al.*[418]	Unexplained infertility	5	187	1	209
Sharshiner *et al.*[419]	Recurrent pregancy loss	1	115	1	115
Tiboni *et al.*[420]	Infertility	5	195	2	198
Vanciková *et al.*[401]	Infertility	1	362	6	1306
Zahmatkeshan[421]	Infertility	14	85	1	197
Summary					

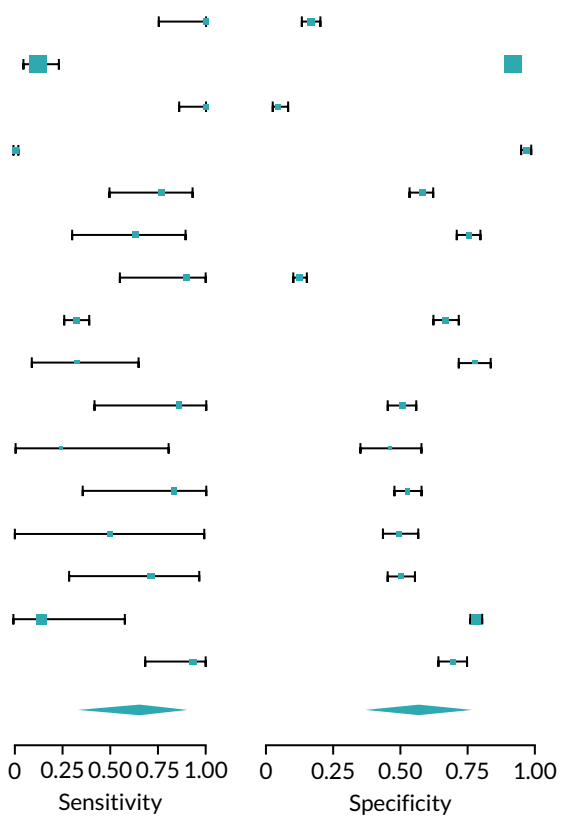

FIGURE 47 Subfertility or recurrent pregnancy loss. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abu-Zekry *et al.*[432]	Type 1 diabetes	16	234	8	1492
Adlercreutz *et al.*[433]	Type 1 diabetes	114	548	29	280
Adlercreutz *et al.*[433]	Type 1 diabetes	126	954	16	267
Aktay *et al.*[434]	Type 1 diabetes	15	203	0	117
Baptista *et al.*[435]	Type 1 diabetes	5	99	0	105
Dagdelen *et al.*[426]	Type 1 diabetes	5	60	1	64
Djurić *et al.*[436]	Type 1 diabetes	9	112	1	124
Frohnert *et al.*[437]	Type 1 diabetes	124	129	71	70
Gurau *et al.*[438]	Type 1 diabetes	4	107	1	160
Güvenç *et al.*[427]	Type 1 diabetes	4	96	0	80
Hansson *et al.*[439]	Type 1 diabetes	17	152	2	94
Hanukoglu *et al.*[428]	Type 1 diabetes	9	100	10	1561
Heikkilä *et al.*[321]	Type 1 diabetes	1	55	68	6795
Hujoel *et al.*[290]	Type 1 diabetes	6	3	394	397
Jaeger *et al.*[445]	Type 1 diabetes	19	178	7	143
Kanungo *et al.*[446]	Type 1 diabetes	11	63	3	119
Krause *et al.*[440]	Type 1 diabetes	0	57	0	140
Kurien *et al.*[429]	Type 1 diabetes	37	963	12	1188
Lampasona *et al.*[448]	Type 1 diabetes	25	262	1	212
Mohammed *et al.*[424]	Type 1 diabetes	30	270	1	299
Not *et al.*[443]	Type 1 diabetes	28	463	10	3990
Picarelli *et al.*[425]	Type 1 diabetes	11	83	0	83
Premawardhana *et al.*[444]	Type 1 diabetes	3	116	1	99
Sari *et al.*[447]	Type 1 diabetes	5	43	0	103
Sharifi *et al.*[449]	Type 1 diabetes	8	92	3	147
Sheikholeslami *et al.*[450]	Type 1 diabetes	1	59	0	60
Shivaprasad *et al.*[430]	Type 1 diabetes	12	246	0	88
Soyucen *et al.*[441]	Type 1 diabetes	2	31	0	41
Velasco *et al.*[442]	Type 1 diabetes	13	129	4	300
Yap *et al.*[276]	Type 1 diabetes	0	1	6	520
Zhao *et al.*[431]	Type 1 diabetes	39	139	1	101
Summary					

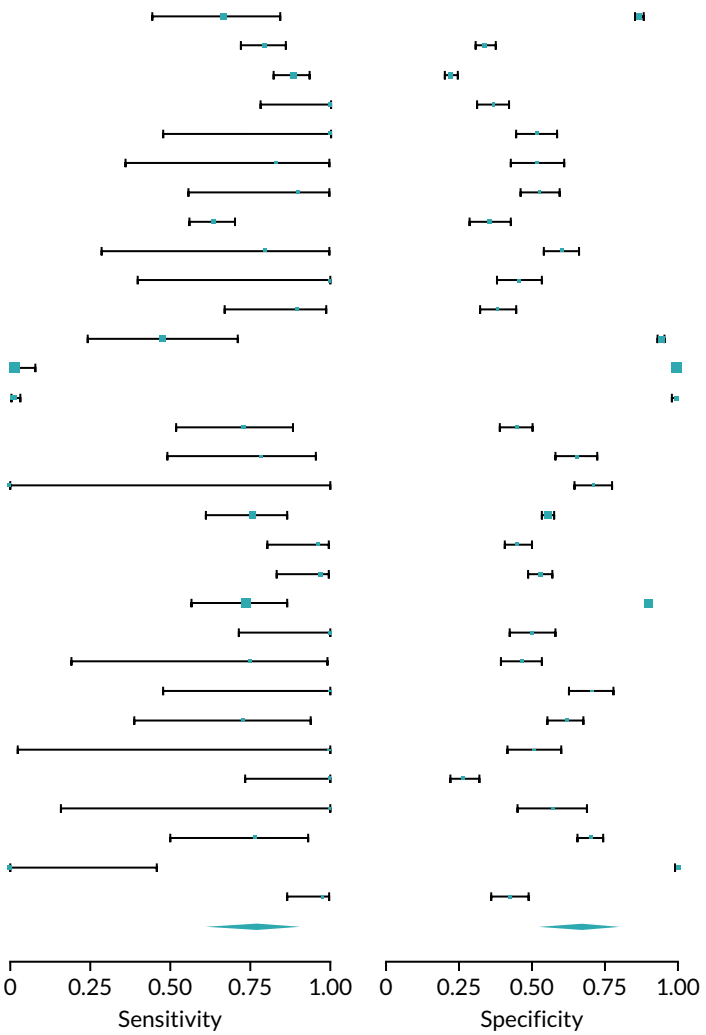

FIGURE 48 Type 1 diabetes. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Heikkilä *et al.*[321]	Type 2 diabetes	1	324	68	6526
Kanungo *et al.*[446]	Type 2 diabetes	23	193	3	119
Kizilgul *et al.*[451]	Type 2 diabetes	2	133	0	115
Lampasona *et al.*[448]	Type 2 diabetes	0	119	1	212
Szepietowska *et al.*[452]	Type 2 diabetes	3	63	3	44
Zhao *et al.*[431]	Type 2 diabetes	5	140	1	101
Summary					

FIGURE 49 Type 2 diabetes. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Abu-Zeid *et al.*[277]	Thyroid disorder	1	8	13	1175
Oana *et al.*[387]	Autoimmune thyroid disease	5	69	0	60
Berti *et al.*[456]	Hashimoto's thyroiditis or Graves' disease	6	166	10	3990
Ch'ng *et al.*[457]	Graves' disease	4	107	1	114
Feighery *et al.*[316]	Graves' disease	1	93	0	30
Guliter *et al.*[458]	Thyroid autoimmunity	6	130	1	118
Hujoel *et al.*[290]	Thyroditis, hypo- or hyperthyroidism	40	29	360	371
Marwaha *et al.*[461]	TPOAbs	15	221	8	228
Marwaha *et al.*[461]	TPOAbs	25	316	12	329
de Melo *et al.*[466]	Thyroid autoimmunity	14	440	2	196
Metzger *et al.*[460]	Thyroid disorder	9	555	54	4015
Miskiewicz *et al.*[455]	Graves' disease	8	224	1	121
Ravaglia *et al.*[453]	Thyroid autoimmunity	11	726	2	598
Ravaglia *et al.*[453]	Thyroid autoimmunity	3	511	1	299
Risan[465]	Free T_4 or TSH	6	41	0	30
Riseh *et al.*[454]	Hashimoto's thyroiditis	9	31	7	35
Sahin *et al.*[462]	Thyroid autoimmunity	2	64	0	66
Sari *et al.*[463]	Thyroid autoimmunity	6	95	0	103
van der Pals *et al.*[464]	TPOAbs	24	48	311	1647
Volta *et al.*[459]	Hashimoto's thyroiditis	7	213	1	249
West *et al.*[359]	Thyroid disorder	7	446	80	6806
Yap *et al.*[276]	Thyroid disorder	0	6	6	515
Zhao *et al.*[431]	Autoimmune and non-autoimmune thyroid disease	3	213	1	101
Summary					

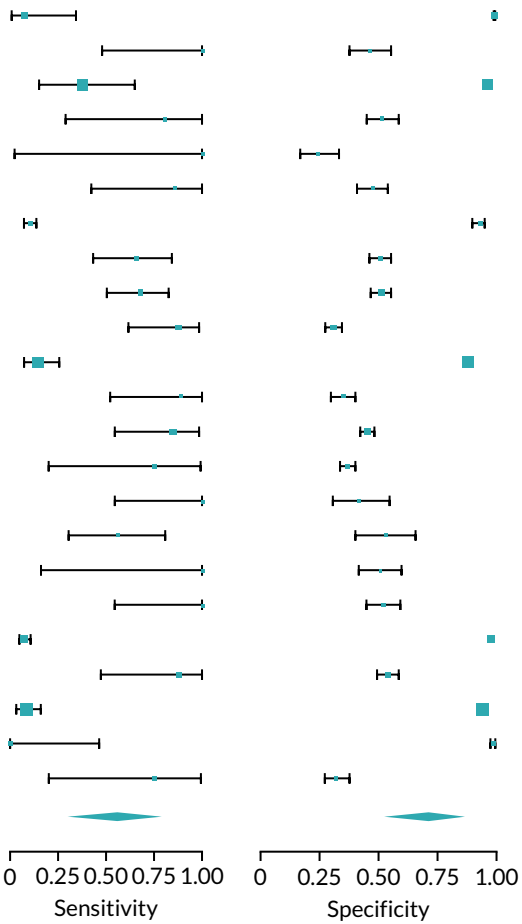

FIGURE 50 Thyroid disease. FN, false negative; FP, false positive; TN, true negative; T_4, thyroxine; TP, true positive; TPOAbs, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

Family history

Reference	Indicator details	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)
Yap *et al.*[276]	CD in family	0	2	6	519
Beser *et al.*[349]	CD in family	0	37	15	3716
Soni *et al.*[346]	CD in family	27	167	3	137
Jansen *et al.*[183]	CD in family	9	626	48	3625
Abu-Zeid *et al.*[277]	FDRs	0	2	14	1181
Choung *et al.*[347]	FDRs	16	1048	5	1059
Cintado *et al.*[350]	FDRs	10	44	0	60
Fasano *et al.*[348]	FDRs	151	3063	27	2818
Fasano *et al.*[348]	FDRs	54	1240	4	1277
Kotze *et al.*[351]	FDRs	18	97	0	126
Stahl *et al.*[293]	FDRs	24	308	218	9423
Nass *et al.*[352]	FDRs and SDRs	15	218	0	100
Utiyama *et al.*[353]	FDRs and SDRs	8	169	0	93
Summary					

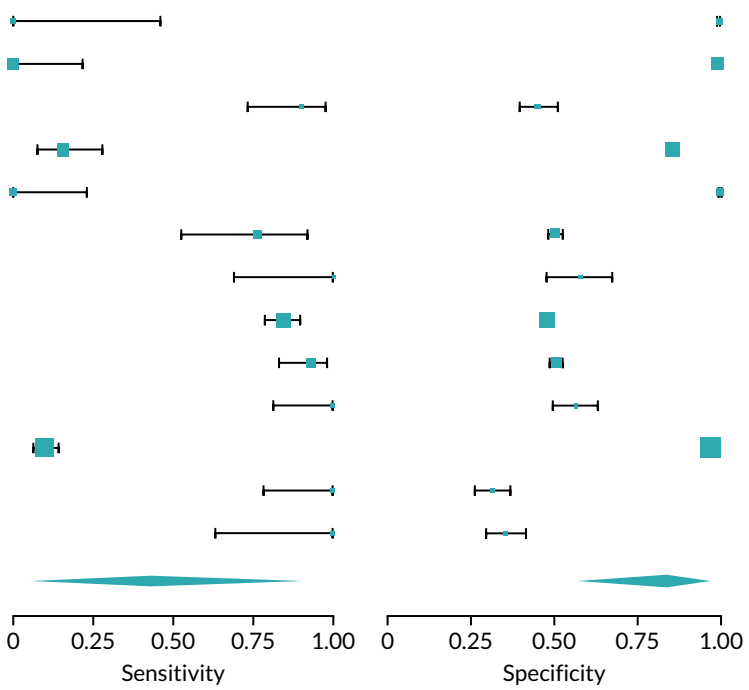

FIGURE 51 Family history of CD. FDR, first-degree relative; FN, false negative; FP, false positive; SDR, second-degree relative; TN, true negative; TP, true positive.

Appendix 7 Subgroup analysis

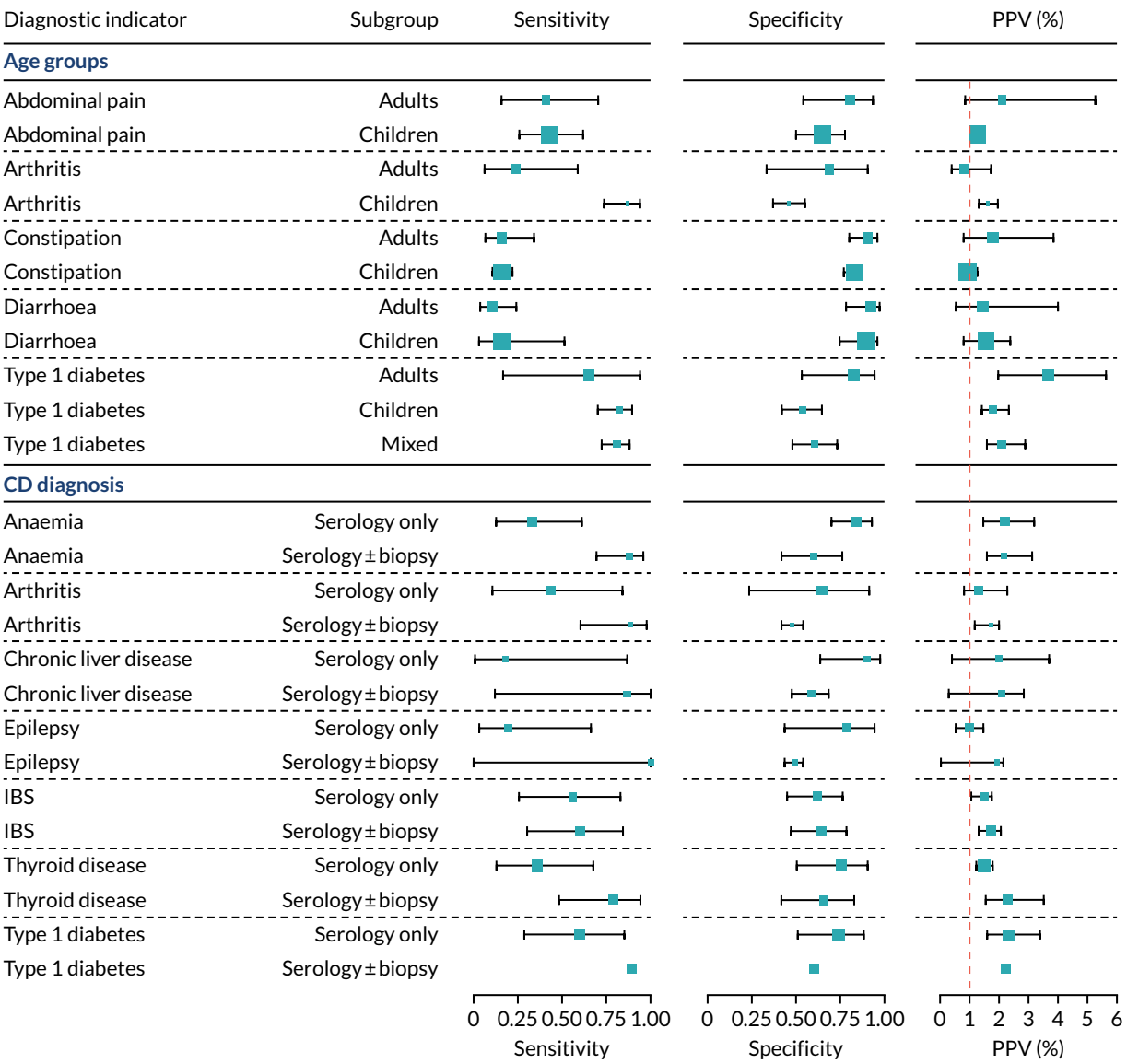

FIGURE 52 Subgroup analysis stratified by age group and CD diagnosis. Note that stratified meta-analysis results are shown per diagnostic indicator. PPVs were calculated for a population with a CD prevalence of 1% (red dotted line) using the estimated sensitivities and specificities from the meta-analyses. The area of the box size is proportional to the total number of participants.

Appendix 8 Sensitivity analysis

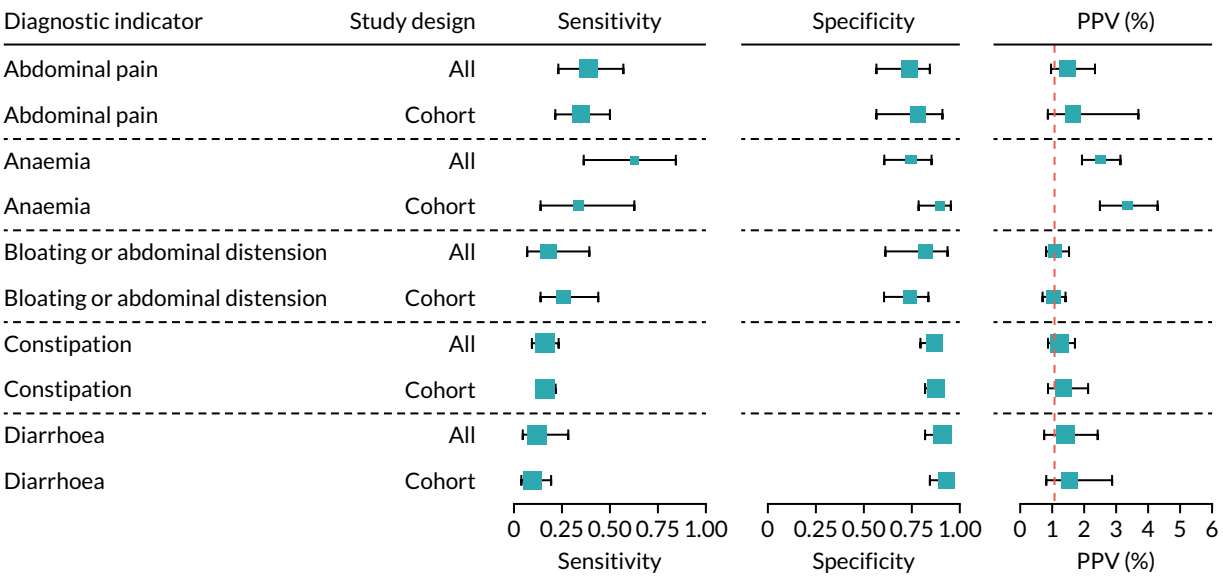

FIGURE 53 Sensitivity analysis restricted to cohort studies. PPVs were calculated for a population with a CD prevalence of 1% (red dotted line) using the estimated sensitivities and specificities from the meta-analyses. The area of the box size is proportional to the total number of participants.

Appendix 9 Candidate diagnostic indicators

TABLE 52 Candidate diagnostic indicator definitions and sources

Diagnostic indicator	Definition (ICPC-2[52] definition, if available)	Diagnostic indicator review	NICE 2015 guidelines[9]	ESPGHAN 2020 guidelines[10]	ESsCD 2019 guidelines[11]
Amenorrhoea	Primary and secondary amenorrhoea (i.e. the absence or cessation of menstruation)			✗	✗
Anaemia	Any IDA (B80), including anaemia due to blood loss Excludes iron deficiency without anaemia (T91)	✗		✗	✗
Arthritis	Includes rheumatoid/seropositive arthritis; allied condition: ankylosing spondylitis; allied condition: juvenile arthritis (L88) Excludes psoriatic arthropathy (L99)	✗		✗	
Attention deficit disorder/cognitive impairment	Includes hyperkinetic disorder, attention deficit disorder, hyperactivity (P81), cognitive impairment				✗
Cardiovascular disease	Includes atherosclerosis/ peripheral vascular disease, arterial embolism/thrombosis/ stenosis; arteriosclerosis; atheroma; endarteritis; gangrene; intermittent claudication; limb ischaemia; Raynaud syndrome; vasospasm (K92); acute myocardial infarction (K75); ischaemic heart disease with angina, angina of effort; angina pectoris; angina with spasm; ischaemic chest pain; unstable angina (K74); ischaemic heart disease without angina, aneurysm of heart; arteriosclerotic/ atherosclerotic heart disease; coronary artery disease; ischaemic cardiomyopathy; old myocardial infarction; silent myocardial ischaemia (K76); stroke/ cerebrovascular accident, apoplexy; cerebral embolism/ infarction/thrombosis/occlusion/ stenosis/haemorrhage; cerebrovascular accident; subarachnoid haemorrhage (K90); transient cerebral ischaemia, basilar insufficiency; drop attacks; transient global amnesia; transient ischaemic attack (K89)	✗			

continued

TABLE 52 Candidate diagnostic indicator definitions and sources (*continued*)

Diagnostic indicator	Definition (ICPC-2[52] definition, if available)	Diagnostic indicator review	NICE 2015 guidelines[9]	ESPGHAN 2020 guidelines[10]	ESsCD 2019 guidelines[11]
Chronic liver disease	Includes liver disease NOS, alcohol hepatitis; cirrhosis; fatty liver; hepatitis NOS; liver failure; portal hypertension (D97); viral hepatitis (D72)	✗		✗	✗
Delayed puberty	Delayed puberty is when boys have no signs of testicular development by 14 years of age, and when girls have not started to develop breasts by 13 years of age, or they have developed breasts, but their periods have not started by 15 years of age (NHS)			✗	
Dental enamel defects	Enamel hypoplasia, dental enamel defects		✗	✗	✗
Down syndrome	Down syndrome		✗	✗	✗
Epilepsy	Includes all types of epilepsy, focal seizures; generalised seizures; grand mal; petit mal; status epilepticus (N88), convulsion (N0)7	✗			✗
Failure to thrive	Includes failure to thrive, physiological delay growth (T10) Excludes delayed milestones (P22); learning disorder (P24); mental retardation (P85); delayed puberty (T99)		✗	✗	✗
Fatigue	Includes weakness/tiredness general, chronic fatigue syndrome; exhaustion; fatigue; lassitude; lethargy; post viral fatigue (A04) Excludes malaise/feeling ill (A05); drowsiness (A29); heat exhaustion (A88); jetlag (A88); systemic lupus erythematosus disturbance (P06)		✗	✗	✗
First-degree relatives with CD	Parent, sibling or child with CD	✗	✗	✗	✗
Fractures	Includes radius/ulna fracture (L72), tibia/fibula fracture (L73), hand/foot bone fracture (L74), femur fracture (L75), other fractures (76) Excludes pathological fracture (osteoporosis) L95; pathological fracture NOS (L99); non-union (L99)	✗		✗	

TABLE 52 Candidate diagnostic indicator definitions and sources (*continued*)

Diagnostic indicator	Definition (ICPC-2[52] definition, if available)	Diagnostic indicator review	NICE 2015 guidelines[9]	ESPGHAN 2020 guidelines[10]	ESsCD 2019 guidelines[11]
GI symptoms	Includes abdominal colic; abdominal cramps/discomfort/ pain NOS; infant colic (D01), heartburn, acidity, water brash (D03), epigastric pain (D02); dyspepsia/indigestion (D07); oesophagitis/reflux (D84), flatulence/gas/belching (D08), bloating; eructation; gas pains; gaseous distension; passing wind; abdominal distension (abdominal swelling without mass) (D25), constipation, faecal impaction (D12), diarrhoea, frequent/loose bowel movements; watery stools (D11), vomiting, emesis; hyperemesis; retching (D10); nausea (D09) Excludes epigastric ache (D02); other localised abdominal pain (D06); biliary colic (D98); renal colic (U14); dysmenorrhoea (X02), abdominal mass (D24); ascites (D29), ileus (D99), melaena (D15); change in faeces/bowel movements (D18), haematemesis (D14); vomiting in pregnancy (W05), feelings of overeating (D02); alcohol-induced nausea (P16); loss of appetite (T03); nausea in pregnancy (W05)	✗	✗	✗	✗
Hyposplenism or functional asplenia	Hyposplenism (reduced splenic functioning) or functional asplenia (absence of normal spleen function), including splenectomy				✗
IgA deficiency	IgA deficiency			✗	✗
IgA nephropathy	Also known as Berger's disease				✗
Inflammatory bowel disease	Inflammatory bowel disease is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterised by chronic inflammation of the GI tract	✗			✗
Iron, vitamin B_{12} or folate deficiency	Includes anaemia, vitamin B_{12}/ folate deficiency, macrocytic anaemia, pernicious anaemia (B81); vitamin B_{12} deficiency without anaemia (T91), iron deficiency without anaemia		✗		
Irritability	Includes feeling/behaving irritable/angry, agitation NOS; restlessness NOS (P04) Excludes overactive child (P22); irritability in partner (Z13)			✗	

continued

TABLE 52 Candidate diagnostic indicator definitions and sources (*continued*)

Diagnostic indicator	Definition (ICPC-2[52] definition, if available)	Diagnostic indicator review	NICE 2015 guidelines[9]	ESPGHAN 2020 guidelines[10]	ESsCD 2019 guidelines[11]
IBS	Includes IBS (D93), spastic colon	✗	✗		✗
	Excludes GI infection (D70); gastroenteritis-presumed infection (D73); regional enteritis (D94); allergic/dietetic/toxic gastroenteritis/colitis (D99); vascular insufficiency of gut (D99); psychogenic diarrhoea (P75)				
Migraine or headaches	Includes headache, post-traumatic headache (N01); migraine (N89); cluster headache (N90); tension headache (N95)	✗			✗
	Excludes cervicogenic headache (L83); face pain (N03); atypical facial neuralgia (N99); sinus pain (R09); post-herpetic pain (S70)				
Mood disorders	Includes depressive disorder, depressive neurosis/psychosis; mixed anxiety and depression; puerperal/postnatal depression; reactive depression (P76); affective psychosis, bipolar disorder; hypomania; mania; manic depression (P73)				✗
Multiple sclerosis	Includes multiple sclerosis, disseminated sclerosis (N86)	✗			
Neuropathy or ataxia	Includes peripheral neuritis/ neuropathy, acute infective polyneuropathy; diabetic neuropathy (double code with T89, T90); Guillain–Barré syndrome; nerve lesion; neuropathy; phantom limb (N94); neurological symptom/complaint other, ataxia; gait abnormality; limping; meningism (N29)		✗	✗	✗
Osteoporosis	Includes osteoporosis, pathological fracture due to osteoporosis (L95); osteomalacia, osteopenia, decreased bone mineralisation	✗	✗	✗	✗
Pancreatitis	Unexplained acute or chronic pancreatitis				✗
Psoriasis	Psoriasis (S91)	✗			✗
Pulmonary haemosiderosis	Pulmonary haemosiderosis				✗
Raised liver enzymes	Elevated liver enzymes (including alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase	✗	✗	✗	✗

TABLE 52 Candidate diagnostic indicator definitions and sources (*continued*)

Diagnostic indicator	Definition (ICPC-2[52] definition, if available)	Diagnostic indicator review	NICE 2015 guidelines[9]	ESPGHAN 2020 guidelines[10]	ESsCD 2019 guidelines[11]
Severe or persistent mouth ulcers	Severe or persistent mouth ulcers including recurrent aphthous stomatitis		✗	✗	✗
Subfertility or recurrent miscarriage	Includes abortion spontaneous, abortion complete/incomplete/missed/habitual, miscarriage (W82); infertility/subfertility female, primary and secondary sterility (W15)	✗	✗		✗
Systemic lupus erythematosus	Systemic lupus erythematosus	✗			
Thyroid disease	Thyroiditis, autoimmune thyroiditis, hypothyroidism, hyperthyroidism, Graves' disease, goitre, Hashimoto's thyroiditis, painless thyroiditis (silent thyroiditis), subacute thyroiditis, Graves' disease excluding postpartum thyroiditis	✗	✗	✗	✗
Turner syndrome	Turner syndrome		✗	✗	✗
Type 1 diabetes	Type 1 diabetes, includes juvenile diabetes or insulin-dependent diabetes (T89)	✗	✗	✗	
Type 2 diabetes	Type 2 diabetes, includes diabetes NOS; late-onset diabetes; type 2 diabetes (T90)	✗			
Weight loss	Includes weight loss, cachexia (T08) Excludes anorexia nervosa (P86)	✗	✗	✗	✗
Williams–Beuren syndrome	Also known as Williams syndrome			✗	

NOS, not otherwise specified.

Appendix 10 Patient flow diagrams

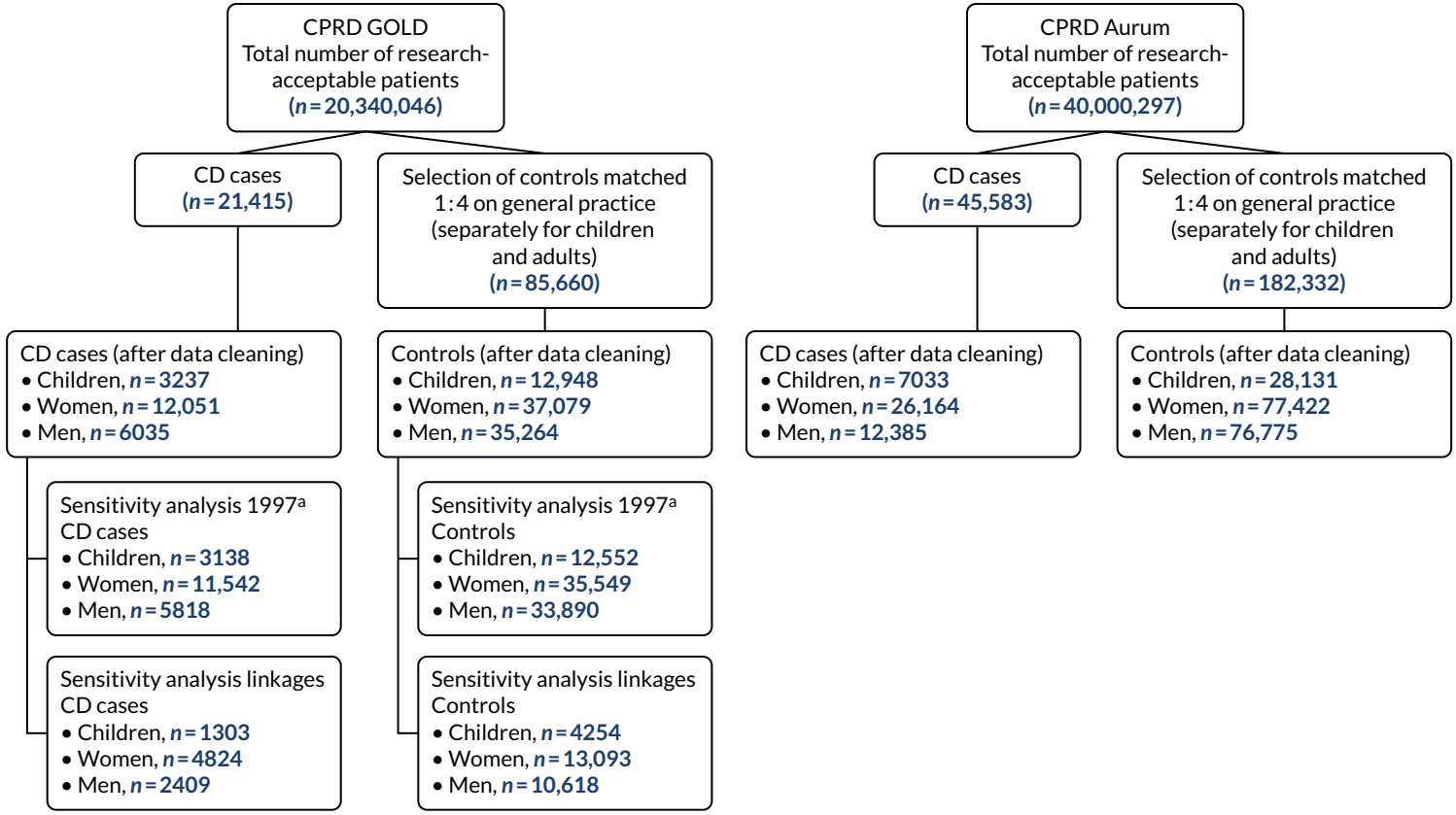

FIGURE 54 Patient flow diagrams for the development (CPRD GOLD) and external validation (CPRD Aurum) data sets. a, This sensitivity analysis was restricted to patients diagnosed after 1997 because in this year IgA tTG tests were first developed, which are now the preferred serological test for screening for CD.[a]

Appendix 11 Model coefficients and odds ratios

TABLE 53 Children: model coefficients and odds ratios with and without shrinkage applied

Selected predictors	Coefficients (apparent model)	200 bootstrapped samples, median (IQR) (internal validation)	Coefficients without shrinkage (apparent model)	Odds ratios (apparent model)		Unadjusted coefficients	Unadjusted odds ratios
				After shrinkage	Without shrinkage		
(Intercept)	−5.119	−5.127 (−5.146 to −5.108)	−5.119				
Type 1 diabetes	4.153	4.182 (4.062–4.278)	4.794	63.648	120.796	4.318	75.038
Turner syndrome	3.949	3.908 (3.715–4.084)	11.243	51.866	76,309.782	13.955	1,149,686.667
IgA deficiency	3.210	3.185 (2.287–3.563)	10.770	24.789	47,560.457	12.954	422,523.354
First-degree relatives with CD	3.100	3.109 (3.037–3.172)	3.361	22.196	28.808	3.167	23.736
Anaemia	2.645	2.618 (2.522–2.751)	2.881	14.080	17.841	2.850	17.288
Down syndrome	2.429	2.428 (2.096–2.763)	2.724	11.344	15.240	2.490	12.061
Weight loss	2.316	2.302 (2.142–2.485)	2.563	10.135	12.972	2.811	16.627
Thyroid disorders	2.144	2.185 (2.000–2.395)	2.361	8.536	10.601	2.742	15.518
Iron, vitamin B_{12} or folate deficiency	2.016	2.013 (1.704–2.363)	2.288	7.508	9.860	2.872	17.672
Delayed puberty	1.995	1.997 (1.537–2.577)	2.464	7.353	11.756	2.997	20.025
Failure to thrive	1.382	1.398 (1.215–1.540)	1.517	3.981	4.558	1.888	6.606
Arthritis	1.318	1.371 (0.949–1.738)	1.525	3.737	4.596	1.725	5.613
IBS	1.127	1.135 (0.934–1.377)	1.246	3.087	3.476	1.765	5.842
Fatigue (count 1 year)	1.111	1.090 (0.967–1.233)	1.249	3.036	3.487	2.139	8.491
GI symptoms (count 1 year)	0.794	0.792 (0.775–0.817)	0.854	2.213	2.348	1.023	2.782
Fatigue	0.613	0.605 (0.500–0.698)	0.603	1.846	1.827	1.638	5.145
GI symptoms	0.582	0.584 (0.550–0.613)	0.603	1.790	1.828	1.304	3.684
Mood disorders	0.363	0.343 (0.250–0.448)	0.389	1.437	1.476	0.829	2.291
Age	0.011	0.011 (0.007–0.014)	0.014	1.011	1.014	−0.007	0.993
Sex (male)	−0.477	−0.472 (−0.502 to −0.447)	−0.537	0.621	0.584	−0.585	0.557

TABLE 54 Women: model coefficients and odds ratios with and without shrinkage applied

Selected predictors	Coefficients (apparent model)	200 bootstrapped samples, median (IQR)	Coefficients without shrinkage (apparent model)	Odds ratios (apparent model)		Unadjusted coefficients	Unadjusted odds ratios
				After shrinkage	Without shrinkage		
(Intercept)	−5.063	−5.062 (−5.080 to −5.042)	−5.057				
First-degree relative with CD	2.459	2.449 (2.378–2.517)	2.519	11.689	12.413	2.505	12.244
Anaemia	1.630	1.635 (1.605–1.661)	1.659	5.102	5.252	1.914	6.780
Iron, vitamin B_{12} or folate deficiency	1.323	1.383 (0.554–2.113)	1.348	3.753	3.851	1.810	6.110
Type 1 diabetes	1.277	1.337 (1.293–1.375)	1.312	3.584	3.714	1.487	4.424
Down syndrome	1.163	1.269 (1.161–1.358)	1.256	3.198	3.512	1.124	3.077
IgA deficiency	1.127	1.170 (0.765–1.596)	1.266	3.087	3.545	2.223	9.235
Turner syndrome	1.080	1.057 (0.422–1.681)	1.186	2.944	3.275	1.635	5.129
Osteoporosis	1.028	1.040 (1.000–1.077)	1.054	2.797	2.869	1.158	3.184
Weight loss	0.910	0.895 (0.848–0.950)	0.929	2.485	2.533	1.463	4.319
Mouth ulcers (count 1 year)	0.857	0.841 (0.767–0.907)	0.886	2.357	2.425	1.196	3.307
Systemic lupus erythematosus	0.699	0.698 (0.532–0.856)	0.737	2.011	2.090	1.077	2.936
GI symptoms (count 1 year)	0.604	0.604 (0.594–0.615)	0.616	1.829	1.852	0.760	2.138
Thyroid disorders	0.599	0.598 (0.563–0.629)	0.614	1.821	1.848	0.847	2.333
Fatigue (count 1 year)	0.545	0.544 (0.518–0.571)	0.559	1.725	1.748	0.923	2.517

continued

TABLE 54 Women: model coefficients and odds ratios with and without shrinkage applied (*continued*)

Selected predictors	Coefficients (apparent model)	200 bootstrapped samples, median (IQR)	Coefficients without shrinkage (apparent model)	Odds ratios (apparent model)		Unadjusted coefficients	Unadjusted odds ratios
				After shrinkage	Without shrinkage		
IBS	0.478	0.474 (0.450–0.505)	0.488	1.613	1.629	0.698	2.010
Chronic liver disease	0.326	0.324 (0.245–0.383)	0.341	1.386	1.406	0.739	2.094
Epilepsy	0.258	0.252 (0.232–0.268)	0.277	1.295	1.319	0.614	1.848
GI symptoms	0.249	0.251 (0.173–0.360)	0.243	1.283	1.275	1.017	2.765
Fractures (count 1 year)	0.196	0.203 (0.167–0.241)	0.205	1.217	1.228	0.561	1.752
Cardiovascular disease	0.196	0.190 (0.139–0.222)	0.206	1.216	1.229	0.370	1.448
Neuropathy or ataxia	0.179	0.178 (0.074–0.311)	0.203	1.196	1.225	0.703	2.020
Fatigue	0.153	0.151 (0.127–0.178)	0.149	1.165	1.160	0.853	2.347
Inflammatory bowel disease	0.138	0.112 (0.000–0.227)	0.153	1.148	1.165	0.952	2.591
Psoriasis	0.048	0.047 (0.000–0.097)	0.058	1.050	1.060	0.299	1.349
Age	−0.006	−0.006 (−0.006 to −0.005)	−0.006	0.994	0.994	0.001	1.001

TABLE 55 Men: model coefficients and odds ratios with and without shrinkage applied

Selected predictors	Coefficients (apparent model)	200 bootstrapped samples, median (IQR)	Coefficients without shrinkage (apparent model)	Odds ratios (apparent model)		Unadjusted coefficients	Unadjusted odds ratios
				After shrinkage	Without shrinkage		
(Intercept)	−5.478	−5.488 (−5.526 to −5.460)	−5.481				
Anaemia	2.685	2.689 (2.632–2.753)	2.727	14.656	15.293	3.148	23.289
First-degree relatives with CD	2.347	2.362 (2.282–2.461)	2.395	10.456	10.969	2.210	9.116
Iron, vitamin B_{12} or folate deficiency	1.810	1.828 (1.754–1.917)	1.841	6.112	6.302	2.632	13.902
Type 1 diabetes	1.746	1.749 (1.650–1.868)	1.787	5.730	5.972	1.840	6.297
Osteoporosis	1.554	1.549 (1.433–1.673)	1.588	4.730	4.892	1.992	7.330
Weight loss	1.490	1.489 (1.431–1.552)	1.514	4.438	4.545	2.154	8.619
Down syndrome	1.293	1.344 (0.856–1.813)	1.405	3.643	4.075	1.766	5.847
Mouth ulcers (count year 1)	0.934	0.919 (0.849–0.994)	0.965	2.544	2.624	1.503	4.495
Thyroid disorders	0.910	0.913 (0.753–1.074)	0.928	2.484	2.530	1.499	4.477
GI symptoms (count year 1)	0.787	0.789 (0.772–0.807)	0.799	2.197	2.223	1.037	2.821
IBS	0.709	0.714 (0.651–0.776)	0.728	2.032	2.072	1.240	3.456
Fatigue (count year 1)	0.663	0.652 (0.592–0.714)	0.680	1.941	1.974	1.178	3.248
GI symptoms	0.448	0.442 (0.414–0.472)	0.447	1.565	1.563	1.348	3.850
Mouth ulcers	0.412	0.401 (0.305–0.514)	0.427	1.510	1.533	1.118	3.059
Psoriasis	0.335	0.339 (0.265–0.401)	0.354	1.398	1.425	0.671	1.956
Chronic liver disease	0.321	0.321 (0.236–0.396)	0.338	1.378	1.402	0.957	2.604
Epilepsy	0.259	0.290 (0.147–0.384)	0.291	1.296	1.338	0.672	1.958
Cardiovascular disease	0.253	0.243 (0.214–0.282)	0.257	1.288	1.293	0.975	2.651
Fatigue	0.185	0.186 (0.136–0.233)	0.183	1.203	1.201	1.077	2.936
Age	0.010	0.011 (0.010–0.011)	0.011	1.010	1.011	0.023	1.023

Appendix 12 Calibration curves

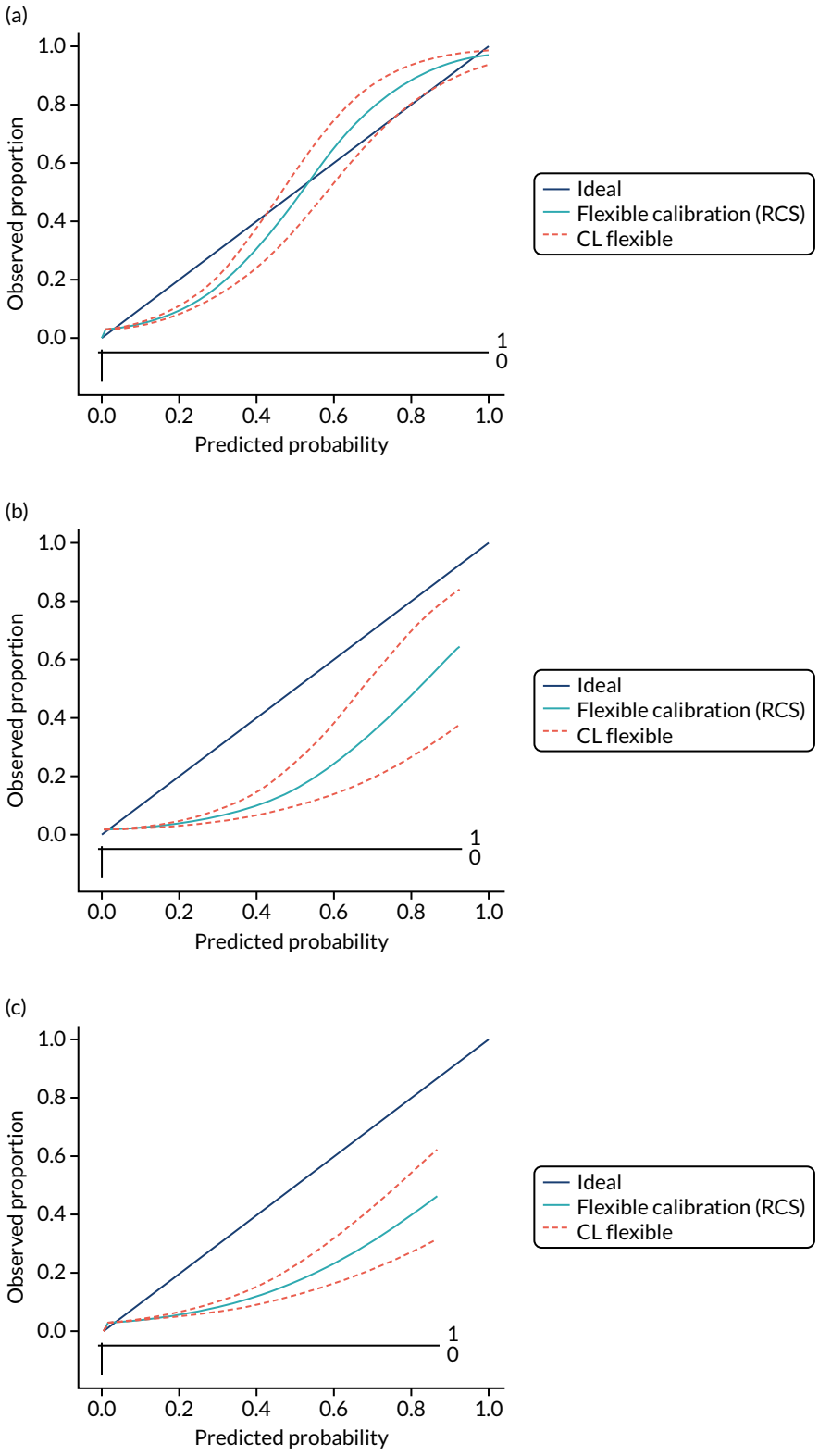

FIGURE 55 Calibration curves model development and external validation. (a) Children: development sample; (b) children: external validation; (c) women: developmental sample; (d) women: external validation; (e) men: developmental sample; and (f) men: external validation. CL, confidence limits; RCS, restricted cubic splines. (*continued*)

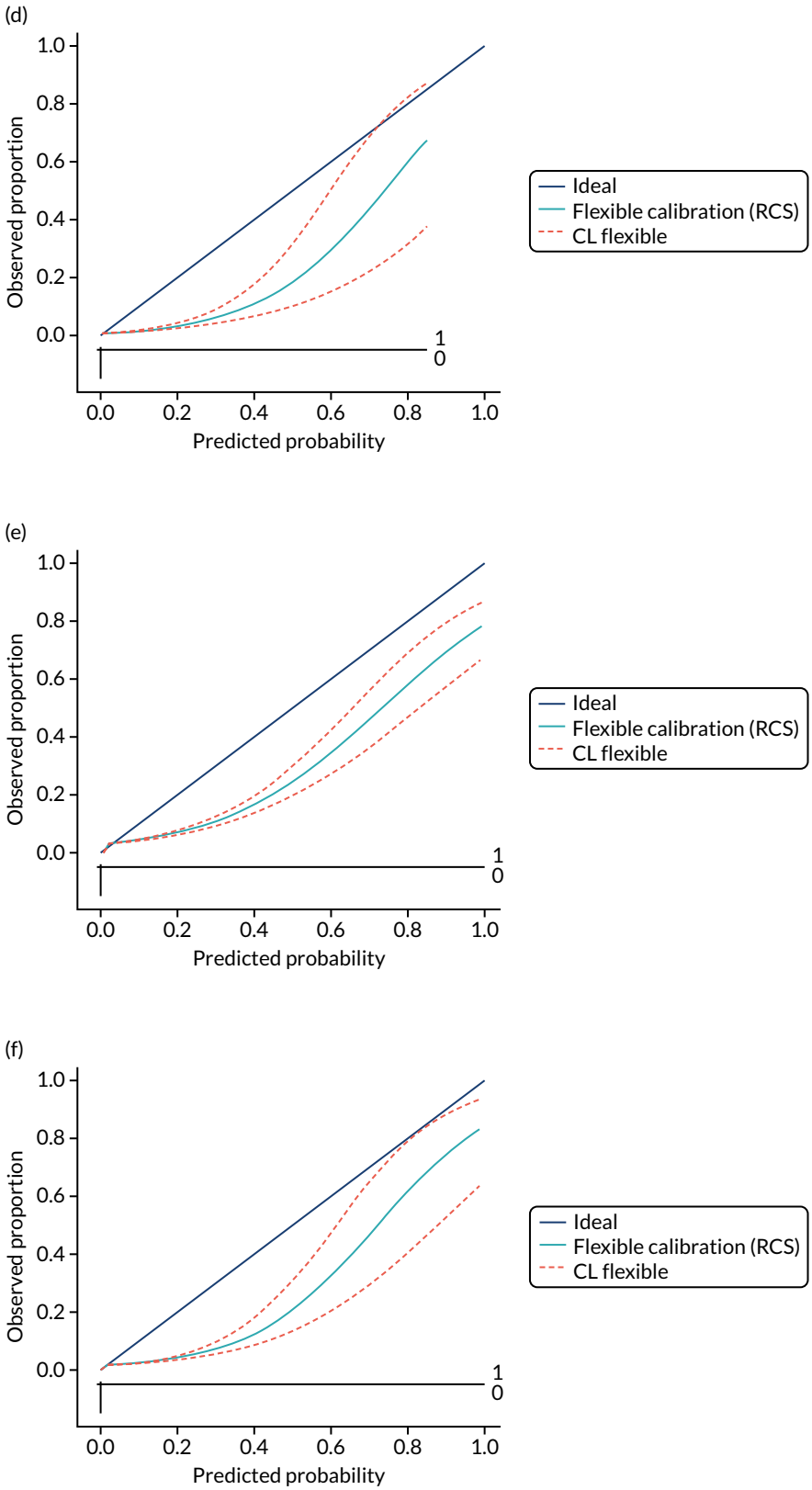

FIGURE 55 Calibration curves model development and external validation. (a) Children: development sample; (b) children: external validation; (c) women: developmental sample; (d) women: external validation; (e) men: developmental sample; and (f) men: external validation. CL, confidence limits; RCS, restricted cubic splines.

Appendix 13 Clinical usefulness in external validation data

TABLE 56 Clinical usefulness in external validation data[a]

Population	Threshold	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	CD patients missed (%)
Children	0	100	9900	0	0	100.0	0	1.0	NA	0
	0.0038	94	9179	6	721	93.5	7.3	1.0	99.1	6.5
	0.0042	75	6297	25	3603	74.6	36.4	1.2	99.3	25.4
	0.0077	13	402	87	9498	12.6	95.9	3.0	99.1	87.4
	0.0170	10	159	90	9741	10.0	98.4	5.9	99.1	90
	0.0800	5	38	95	9862	5.2	99.6	12.1	99.0	94.8
Women	0	100	9900	0	0	100.0	0	1.0	NA	0
	0.0053	32	2327	68	7574	32.2	76.5	1.4	99.1	67.8
	0.0062	14	683	86	9217	14.3	93.1	2.0	99.1	85.7
	0.0233	7	158	93	9742	7.2	98.4	4.5	99.1	92.8
	0.1070	2	20	98	9880	1.7	99.8	7.1	99.0	98.3
	0.7550	0	0	100	9900	0.0	100.0	6.2	99.0	100
Men	0	100	9900	0	0	100.0	0	1.0	NA	0
	0.007	64	4623	36	5277	64.3	53.3	1.4	99.3	35.7
	0.008	42	2376	58	7524	41.6	76.0	1.7	99.2	58.4
	0.0185	11	228	89	9672	10.8	97.7	4.5	99.1	89.2
	0.0610	6	69	94	9831	6.3	99.3	8.2	99.1	93.7
	0.2820	2	10	98	9890	2.0	99.9	14.2	99.0	98

FN, false negative; FP, false positive; NA, not applicable; NPV, negative predictive value; TN, true negative; TP, true positive.
a In a population of 10,000 people.

Appendix 14 Model performance after including ethnicity and deprivation as predictions

TABLE 57 Model performance after including ethnicity and deprivation as predictions

Data	Apparent model performance		Updated model performance
	Original data set (CPRD GOLD)	CPRD GOLD linked with HES	CPRD GOLD linked with HES
Children			
R^2	0.407	0.422	0.426
Brier score	0.167	0.181	0.113
c-statistic	0.821	0.824	0.824
Calibration intercept[a]	0.147	−0.467	−3.483
Calibration slope[a]	0.964	0.978	0.941
Women			
R^2	0.237	0.272	0.276
Brier score	0.227	0.244	0.153
c-statistic	0.756	0.778	0.779
Calibration intercept[a]	−0.161	−0.307	−3.729
Calibration slope[a]	0.822	0.816	0.818
Men			
R^2	0.286	0.300	0.301
Brier score	0.122	0.153	0.113
c-statistic	0.798	0.792	0.793
Calibration intercept[a]	−0.505	−0.768	−3.228
Calibration slope[a]	0.934	0.802	0.843

a Calibration statistics were estimated using an inflated control group to adjust for sampling frequency.

Appendix 15 Association of candidate predictors with coeliac disease

TABLE 58 Association of candidate predictors with CD: complete-case univariable analysis

Candidate predictor	Coefficient (95% CI)	*p*-value	*n*
Type 1 diabetes	2.86 (−0.20 to 5.92)	0.067	2697
Anaemia	0.96 (−0.14 to 2.06)	0.088	5077
Thyroid disorders	0.37 (−2.45 to 3.18)	0.799	3364
GI symptom count			
1	−0.38 (−2.01 to 1.26)	0.651	4168
2–4	0.58 (−1.06 to 2.23)	0.488	4168
Male	−0.78 (−1.39 to −0.17)	0.013	5108
Fatigue	−0.02 (−0.74 to 0.70)	0.951	3967
Mouth ulcers	−0.16 (−1.21 to 0.89)	0.765	2071
GI symptoms	−0.26 (−1.54 to 1.03)	0.695	4188
Mood disorders	−0.63 (−1.73 to 0.47)	0.262	4222
Age	−1.41 (−3.45 to 0.63)	0.176	5117

Appendix 16 Search strategy for diagnostic accuracy review (see *Chapter 5*)

MEDLINE search strategy. This strategy was adapted to run on Embase. The Cochrane Library, KSR Evidence and Web of Science were also searched.

Date range searched: 1997 to April 2021.

1. Celiac Disease/
2. ((coeliac or celiac) adj4 (disease or sprue or syndrome)).tw.
3. ((nontropical or non tropical) adj4 sprue).tw.
4. ((gluten or glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
5. (gluten adj4 enteropath*).tw.
6. or/1-5
7. Serologic Tests/
8. ((serologic or serological) adj4 test*).tw.
9. 7 or 8
10. (endomysi* adj4 antibod*).tw.
11. (immunoglobulin adj4 (endomysi* or anti-endomysi* or antiendomysi* or anti endomysi*)).tw.
12. ((anti-endomysi* or antiendomysi* or anti endomysi*) adj antibod*).tw.
13. ((iga or igg) adj4 (endomysi* or anti-endomysi* or antiendomysi* or anti endomysi*)).tw.
14. (iga-ema or igg-ema).tw.
15. ((EMA or AGA) and antibod*).tw.
16. or/10-15
17. transglutaminases/
18. (((anti-tissue or antitissue or anti tissue) adj4 transglutaminase) and antibod*).tw.
19. ((iga or igg or immunoglobulin) adj4 transglutaminase).tw.
20. ((anti-human or antihuman or anti human or tissue) adj4 transglutaminase adj4 antibod*).tw.
21. (anti-httg or anti-htg or tTg).tw.
22. or/17-21
23. ((gliadin or antigliadin or anti-gliadin or anti gliadin) adj4 antibod*).tw.
24. ((igg or iga or immunoglobulin) adj4 gliadin).tw.
25. ((igg or iga or immunoglobulin) adj4 (antigliadin or anti-gliadin or anti gliadin)).tw.
26. (elisa adj4 test*).tw.
27. Gliadin/and Immunoglobulins/
28. or/23-27
29. HLA-DQ Antigens/or HLA-DR3 Antigen/
30. (human adj3 (leukocyte* or leucocyte*) adj3 antigen*).tw.
31. (hla adj3 typing).tw.
32. ((dr3 or hla) adj4 dq2).tw.
33. ((dr4 or hla) adj4 dq8).tw.
34. or/29-33
35. 9 or 16 or 22 or 28 or 34
36. 6 and 35
37. letter/
38. editorial/
39. news/
40. exp historical article/
41. Anecdotes as topic/
42. comment/
43. case report/

44. (letter or comment* or editorial or case report).ti.
45. or/37-44
46. exp animals/not humans/
47. exp Animals, Laboratory/
48. exp Animal Experimentation/
49. exp Models, Animal/
50. exp rodentia/
51. ((rat or rats or mouse or mice or rodent* or animal* or murine or porcine or feline or canine or dog or dogs or cat or cats or pig or pigs or monkey* or macaque*) not human*).ti.
52. or/46-51
53. 45 or 52
54. 36 not 53.

Appendix 17 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

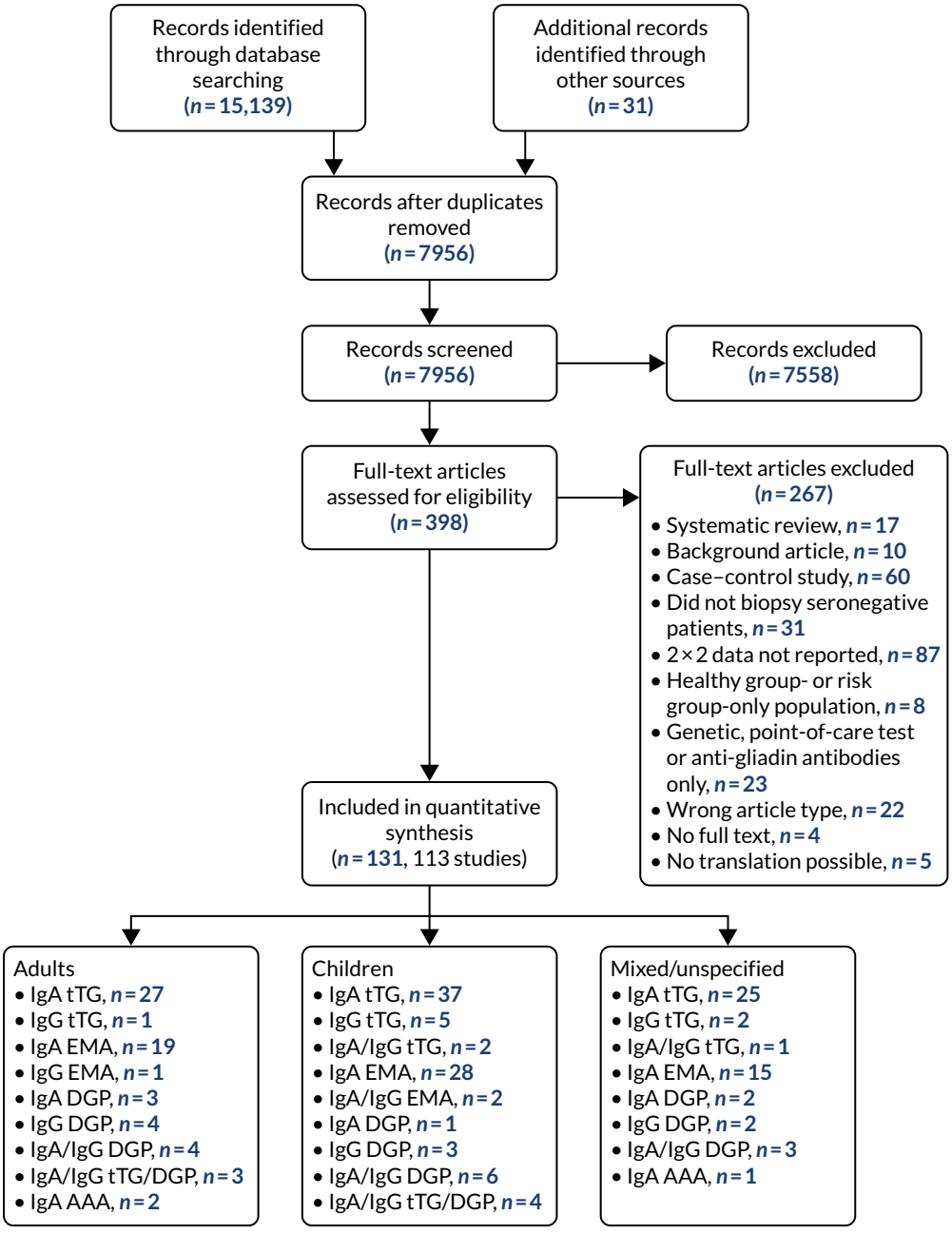

FIGURE 56 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. AAA, anti-actin antibodies.

Appendix 18 Risk-of-bias plots

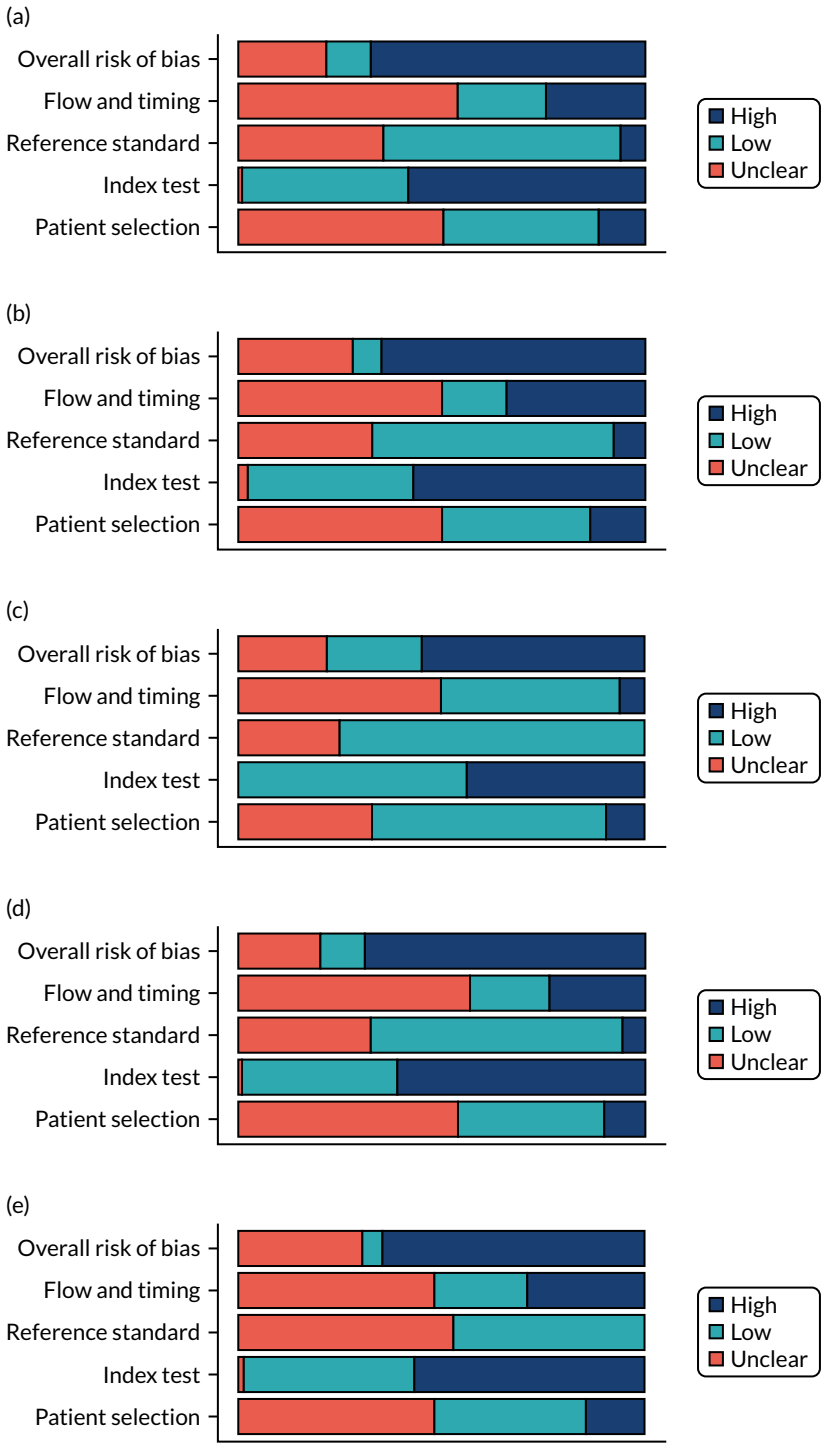

FIGURE 57 Summary risk-of-bias plots for all studies combined, stratified according to age and according to test type. (a) All studies; (b) children; (c) adults; (d) IgA tTG; and (e) IgA EMA.

Appendix 19 Sensitivity and specificity estimates

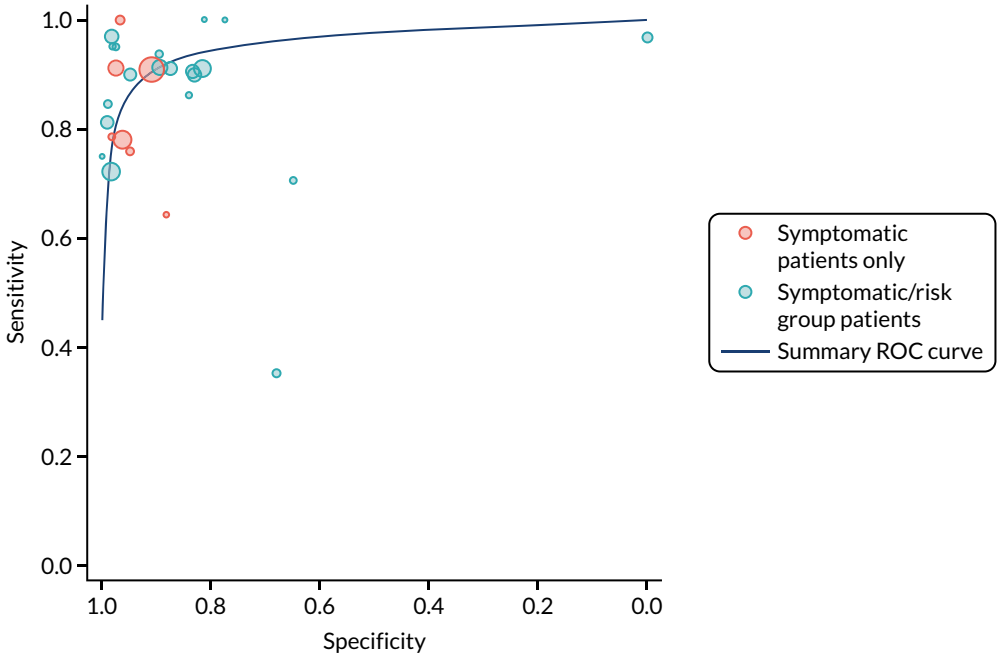

FIGURE 58 Study estimates of IgA tTG sensitivity and specificity for adults plotted in ROC space, stratified by reason for biopsy. SROC curves are estimated from a meta-analysis of all data, across thresholds.

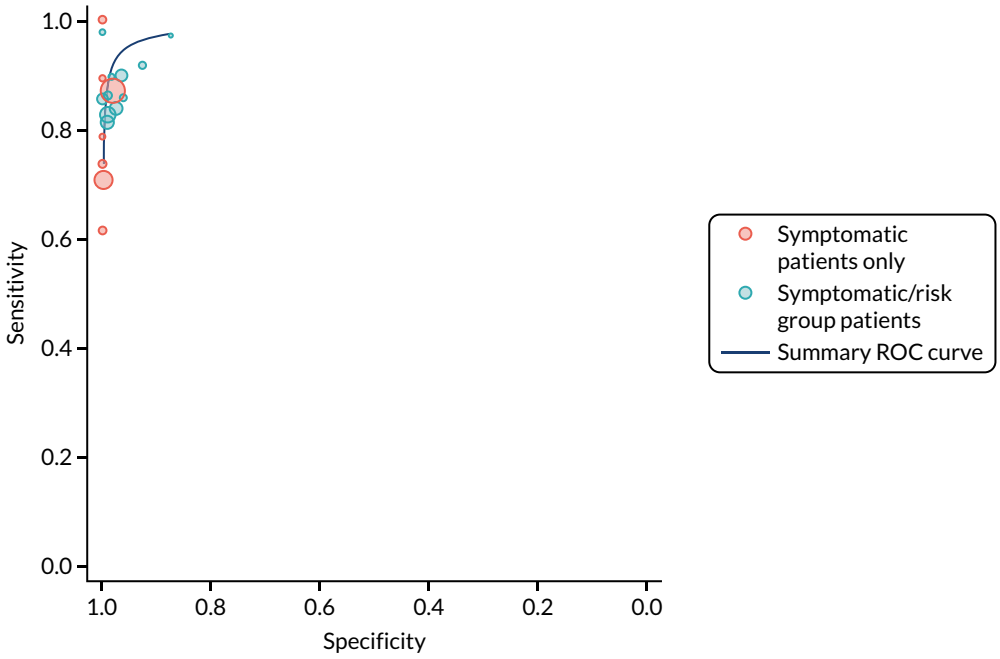

FIGURE 59 Study estimates of IgA EMA sensitivity and specificity for adults plotted in ROC space, stratified by reason for biopsy. SROC curves are estimated from a meta-analysis of all data, across thresholds.

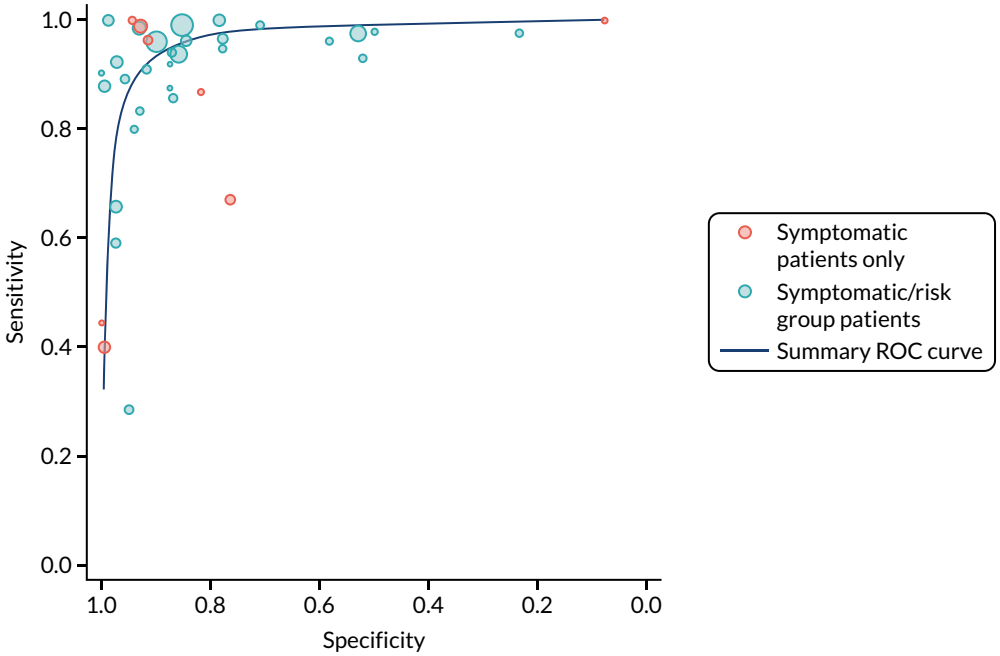

FIGURE 60 Study estimates of IgA tTG sensitivity and specificity for children plotted in ROC space, stratified by reason for biopsy. SROC curves are estimated from a meta-analysis of all data, across thresholds.

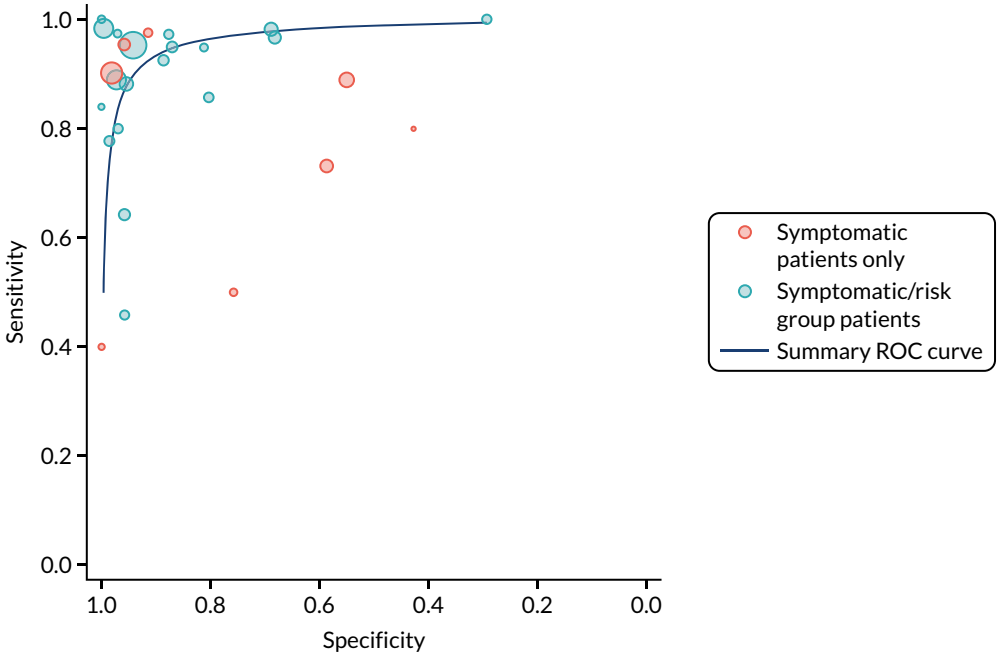

FIGURE 61 Study estimates of IgA EMA sensitivity and specificity for children plotted in ROC space, stratified by reason for biopsy. SROC curves are estimated from a meta-analysis of all data, across thresholds.

Appendix 20 Summary graph of risk of bias

FIGURE 62 Summary risk-of-bias graph for studies evaluating *HLA-DQ2* and/or *-DQ8*.

Appendix 21 Hypothetical scenarios and associated risks of having coeliac disease

BOX 1 Hypothetical scenarios and associated risks of having CD

Scenarios for adults

Scenario 1

You are suffering from episodes of stomach cramps, bloating, diarrhoea and fatigue several times a week over the last 5 years and you have been losing weight unintentionally over the past months. Your symptoms are interfering with your daily life.

- Pre-test probability: 5%.
- Risk of CD if blood test is
  - positive: 33%
  - strong positive (high levels of anti-gluten antibodies): 75%
  - negative: 1%.

Scenario 2

Your 5-year-old son has been diagnosed with CD. You have no symptoms.

- Pre-test probability: 10%.
- Risk of CD if blood test is
  - positive: 50%
  - strong positive: 90%.

Scenario 3

After a recent bone fracture and follow-up testing, you are diagnosed with osteoporosis. Osteoporosis is a health condition that weakens the bones, making them fragile and more likely to break and is a risk condition for CD.

- Pre-test probability: 2%.
- Risk of CD if blood test is
  - positive: 15%
  - strong positive: 55%.

Scenarios for children

Scenario 1

You are suffering from episodes of stomach cramps, bloating, diarrhoea and fatigue several times a week over the last 5 months. These symptoms make it difficult to pay attention in school and to enjoy after-school activities.

- Pre-test probability: 5%.
- Risk of CD if blood test is
  - positive: 33%
  - strong positive: 75%
  - negative: 1%.

BOX 1 Hypothetical scenarios and associated risks of having CD (*continued*)

Scenario 2

You have just found out that one of your parents has CD and needs to follow a lifelong gluten-free diet. You do not have any symptoms yourself.

- Pre-test probability: 10%.
- Risk of CD if blood test is
  - positive: 50%
  - strong positive: 90%.

Scenario 3

After a recent bone fracture and follow-up testing, you are diagnosed with osteoporosis. Osteoporosis is a health condition that weakens the bones, making them fragile and more likely to break.

- Pre-test probability: 2%.
- Risk of CD if blood test is
  - positive: 15%
  - strong positive: 55%.

Appendix 22 Characteristics of survey respondents

TABLE 59 Characteristics of respondents

Characteristic	CD[a] (*N* = 244)	No CD (*N* = 223)	Total (*N* = 468)
Age range (years)*, n *(%)			
0–5	4 (1.6)	9 (4.0)	13 (2.8)
6–11	10 (4.1)	5 (2.2)	15 (3.2)
12–17	15 (6.1)	4 (1.8)	19 (4.1)
18–25	30 (12.3)	22 (9.9)	52 (11.1)
26–40	66 (27.0)	61 (27.4)	127 (27.1)
41–64	93 (38.1)	90 (40.4)	183 (39.1)
≥ 65	26 (10.7)	32 (14.3)	59 (12.6)
Sex*, n *(%)			
Male	29 (11.9)	7 (3.1)	37 (7.9)
Female	211 (86.5)	28 (12.6)	239 (51.1)
Other	1 (0.4)	0 (0)	1 (0.2)
Prefer not to say	2 (0.8)	0 (0)	2 (0.4)
Missing	1 (0.4)	188 (84.3)	189 (40.4)
Ethnicity*, n *(%)			
Asian/Asian British	1 (0.4)	0 (0)	1 (0.2)
Black/African/Caribbean/black British	1 (0.4)	0 (0)	2 (0.4)
Mixed/multiple ethnic groups	6 (2.5)	2 (0.9)	8 (1.7)
Other	3 (1.2)	1 (0.4)	4 (0.9)
White	232 (95.1)	32 (14.3)	264 (56.4)
Missing	1 (0.4)	188 (84.3)	189 (40.4)
Highest education*, n *(%)			
College or university degree	133 (54.5)	26 (11.7)	159 (34.0)
A Level or equivalent	38 (15.6)	4 (1.8)	42 (9.0)
O Level or GCSE or equivalent	33 (13.5)	3 (1.3)	37 (7.9)
Prefer not to say	14 (5.7)	0 (0)	14 (3.0)
Other	18 (7.4)	2 (0.9)	20 (4.3)
Missing	8 (3.3)	188 (84.3)	196 (41.9)
Deprivation score			
Mean (SD)	6.51 (2.50)	6.77 (2.53)	6.52 (2.52)
Median (minimum, maximum)	7.00 (1.00, 10.0)	7.00 (1.00, 10.0)	7.00 (1.00, 10.0)
Missing, *n* (%)	42 (17.2)	197 (88.3)	239 (51.1)

continued

TABLE 59 Characteristics of respondents (*continued*)

Characteristic	CD[a] (*N* = 244)	No CD (*N* = 223)	Total (*N* = 468)
Region*, n *(%)			
East England	21 (8.6)	4 (1.8)	25 (5.3)
East Midlands	14 (5.7)	2 (0.9)	16 (3.4)
Greater London	11 (4.5)	1 (0.4)	12 (2.6)
North East, Yorkshire and Humber	16 (6.6)	1 (0.4)	17 (3.6)
North West	20 (8.2)	0 (0)	20 (4.3)
Northern Ireland	4 (1.6)	1 (0.4)	5 (1.1)
Scotland	14 (5.7)	1 (0.4)	15 (3.2)
South East	28 (11.5)	5 (2.2)	33 (7.1)
South West	80 (32.8)	17 (7.6)	98 (20.9)
Wales	11 (4.5)	1 (0.4)	12 (2.6)
West Midlands	17 (7.0)	0 (0)	17 (3.6)
Missing	8 (3.3)	190 (85.2)	198 (42.3)

GCSE, General Certificate of Secondary Education.
a Confirmed diagnosis with serology test, endoscopy or biopsy.

TABLE 60 Age of respondents who used free-text boxes

	n (%)		
Age range (years)	CD[a] (*N* = 185)	No CD (*N* = 167)	Total (*N* = 353)
0–5	4 (2.2)	6 (3.6)	10 (2.8)
6–11	5 (2.7)	2 (1.2)	7 (2.0)
12–17	8 (4.3)	1 (0.6)	9 (2.6)
18–25	19 (10.3)	15 (9.0)	34 (9.6)
26–40	52 (28.1)	47 (28.1)	99 (28.0)
41–64	77 (41.6)	72 (43.1)	149 (42.2)
≥ 65	20 (10.8)	24 (14.4)	45 (12.8)

a Confirmed diagnosis with serology test, endoscopy or biopsy.

Appendix 23 Themes and subthemes in the open-text answers

TABLE 61 Themes and subthemes in the open-text answers

Themes and subthemes	*n* (%)			
	CD (*N* = 244)	No CD (*N* = 223)	Free-text respondents (*N* = 353)	Total survey respondents (*N* = 468)
Factors prompting CD diagnosis				
Osteoporosis would prompt a desire for testing	21 (8.6)	23 (10.3)	44 (12.5)	44 (9.4)
Would look into CD diagnosis immediately and rule it out early if it was suggested	28 (11.5)	31 (13.9)	59 (16.7)	59 (12.6)
Having an official diagnosis is important	38 (15.6)	11 (4.9)	49 (13.9)	49 (10.5)
Future risks prompt seeking or continuing testing for diagnosis	20 (8.2)	17 (7.6)	37 (10.5)	37 (7.9)
Symptoms decide or prompted getting or continuing seeking diagnosis	16 (6.6)	13 (5.8)	29 (8.2)	29 (6.2)
Family impacts looking into CD diagnosis	13 (5.3)	11 (4.9)	24 (6.8)	24 (5.1)
Does not feel an official diagnosis as important	1 (0.4)	3 (1.3)	4 (1.1)	4 (0.9)
The diagnostic process				
See blood tests as non-invasive or easy to have	94 (38.5)	90 (40.4)	184 (52.1)	184 (39.3)
Feels that a biopsy is necessary for certainty in their diagnosis	77 (31.6)	39 (17.5)	116 (32.9)	116 (24.8)
No symptoms means a biopsy is more necessary for certainty in diagnosis, or easier to have than to continue a GFD with no symptoms	38 (15.6)	38 (17.0)	76 (21.5)	76 (16.2)
If the blood test shows a > 50% chance of having CD, would start a GFD without biopsy	31 (12.7)	45 (20.2)	76 (21.5)	76 (16.2)
Would continue a gluten diet for biopsy	27 (11.1)	14 (6.3)	41 (11.6)	41 (8.8)
6–8 weeks is an acceptable wait time for a biopsy	9 (3.7)	19 (8.5)	28 (7.9)	28 (6.0)
Feels that a biopsy is invasive or unpleasant and would want to avoid it	11 (4.5)	16 (7.2)	27 (7.6)	27 (5.8)
6–8 weeks is unacceptable time to wait for a biopsy	4 (1.6)	9 (4.0)	13 (3.7)	13 (2.8)
How to respond to a negative test result				
Would try a GFD regardless of diagnosis	12 (4.9)	25 (11.2)	37 (10.5)	37 (7.9)
Would ask for further testing or retesting if negative result	16 (6.6)	16 (7.2)	32 (9.1)	32 (6.8)
Doctor's guidance and opinion is important	12 (4.9)	14 (6.3)	26 (7.4)	26 (5.6)
Would accept not having CD	10 (4.1)	16 (7.2)	26 (7.4)	26 (5.6)

continued

TABLE 61 Themes and subthemes in the open-text answers (*continued*)

Themes and subthemes	*n* (%)			
	CD (*N* = 244)	No CD (*N* = 223)	Free-text respondents (*N* = 353)	Total survey respondents (*N* = 468)
Opinions on GFD				
Want definitive diagnosis (biopsy) before starting GFD	63 (25.8)	65 (29.1)	128 (36.3)	128 (27.4)
See if CD symptoms improve with GFD (even if they do not have CD)	23 (9.4)	54 (24.2)	77 (21.8)	77 (16.5)
Have a negative opinion on GFD or see GFD as a big commitment	33 (13.5)	15 (6.7)	48 (13.6)	48 (10.3)
Would start a GFD without a definitive diagnosis	19 (7.8)	17 (7.6)	36 (10.2)	36 (7.7)
Whether or not they live with another who had CD would affect GFD adherence	7 (2.9)	28 (12.6)	35 (9.9)	35 (7.5)
Lowest likelihood (≤ 10% chance) not enough to start a GFD	10 (4.1)	17 (7.6)	27 (7.6)	27 (5.8)
A 50/50 likelihood not enough to start a GFD	7 (2.9)	18 (8.1)	25 (7.1)	25 (5.3)
May consider restarting gluten diet and biopsy if GFD does not work	8 (3.3)	14 (6.3)	22 (6.2)	22 (4.7)
Would start GFD at the lowest likelihood (≤ 10% chance)	1 (0.4)	19 (8.5)	20 (5.7)	20 (4.3)

GFD, gluten-free diet.

Appendix 24 Search strategy for targeted literature review of previous cost-effectiveness models in coeliac disease

Database: Ovid Embase.

Date range searched: 1974 to 2020 week 19.

1. Celiac Disease/ (30,110)
2. C?eliac?.ti,ab,kw. (39,478)
3. or/1-2 (45,026)
4. (c?eliac adj (angiograp* or arter* or axis or plexus or trunk)).ti,ab,kw,hw. (12,349)
5. 3 not 4 (36,020)
6. economic evaluation/or "cost benefit analysis"/or "cost control"/or "cost effectiveness analysis"/or "cost minimization analysis"/or "cost of illness"/or "cost utility analysis"/ (303,574)
7. (economic* adj2 (analys* or benefit* or consequence* or effect* or evaluat* or minimi#ation or saving*)).ti,ab,kw. (47,258)
8. ((cost or costs or costing*) adj2 (analys* or benefit* or consequence* or effective* or estimate* or minimi#ation or saving* or utility or variab*)).ti,ab,kw. (262,232)
9. (cba or cea or cua).ti,ab,kw. (48,623)
10. (budget* or unit cost).ti,ab,kw. (40,257)
11. (expenditure* not energy).ti,ab,kw. (40,404)
12. (value adj2 (money or monetary)).ti,ab,kw. (3249)
13. economic model/ (1993)
14. ((economic? or econometric) adj2 model*).ti,ab,kw. (7359)
15. statistical model/and exp economic aspect/ (21,850)
16. stochastic model/ (14,561)
17. decision tree/ (12,592)
18. (markov* or monte carlo).ti,ab,kw,hw. (86,470)
19. (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (33,681)
20. ((value adj2 information analysis) or (expected value adj3 perfect information) or (expected value adj3 sampl* information)).ti,ab,kw. (529)
21. (microsimulation? or micro-simulation?).mp. (2052)
22. discrete event? simulation?.mp. (1154)
23. or/6-22 (674,534)
24. 5 and 23 (594)
25. limit 24 to conference abstract status (204)
26. 24 not 25 (390)
27. from 26 keep 1-390 (390).

Appendix 25 Economic models

TABLE 62 Summary of economic models

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
Harewood and Murray[195] 2001	USA	To compare the costs of different screening strategies for the detection of CD	GA, EMA	OGD + SBB	Patients with suspected CD (age not reported); modelled three risk groups: low risk with 0.5% prevalence, medium risk with 5% prevalence and high risk with 40% prevalence	Decision tree	Three main branches of tree: GA first vs. EMA first vs. SBB. The GA-first arm modelled the decision to employ EMA following a positive GA test. A positive EMA test resulted in either OGD with SBB or a 2-month clinical trial of a GFD	Not reported	None	EMA is the most economical strategy, compared with the other options, in a low- to medium-risk population. It remains so in DSA provided the prevalence of CD in the tested population is < 42%
Mein and Ladabaum[196] 2004	USA	To explore the cost-effectiveness of different screening strategies for CD among patients with IBS symptoms	tTG only, antibody panel (tTG, IgA GA, IgG GA and IgA deficiency test); upfront endoscopy with biopsy	No screening for CD/ antibody panel	Patients with symptoms of IBS	Decision tree	Four strategies at decision node: no testing, tTG, antibody panel, endoscopy with biopsy	Not reported	Utilities for IBS state, treated CD state following GFD, derived from published SF-36 data in the USA	Serological testing to diagnose CD among patients with a diagnosis of IBS is cost-effective at thresholds of US$50,000 (prevalence of CD 2%) and US$100,000 per QALY gained (prevalence 1.1%)
Spiegel *et al.*[197] 2004	USA	To evaluate different screening strategies for CD among IBS patients with predominant diarrhoea	Testing patients for CD	IBS treatment but no CD screening	Patients with IBS and diarrhoea; sensitivity analyses conducted in different populations with different prevalences	Decision tree followed by Markov model	Two strategies at decision node comparing treatment for IBS with screening for CD to estimate the number of patients receiving appropriate therapy for either IBS or CD; then Markov model with two health states ('symptoms improve' and 'symptoms recur') to estimate transitions between improvement and remission of symptoms once patients started treatment for either IBS or CD; 1-month cycle length for Markov model	10 years	None	Testing for CD is cost-effective vs. IBS therapy among most patients with diarrhoea-predominant IBS (with a CD prevalence of 3.4%). The sensitivity analysis shows that the results are sensitive to the following variables: prevalence of underlying CD, specificity of diagnostic test for CD, probability that GFD improves the symptoms of CD and cost of IBS therapy

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
Shamir *et al.*[198] 2006	USA	Cost-effectiveness analysis to compare screening strategies for CD among adult population	Screening for CD [(1) tTG followed by EMA. (2) tTG. (3) EMA. (4) If no IgA deficiency, tTG followed by EMA; otherwise antigliadin IgG 5. If no IgA deficiency, tTG; otherwise antigliadin IgG 6. If no IgA deficiency, EMA; otherwise antigliadin IgG]	No screening	Adult population (aged > 18 years) symptomatic and high-risk groups	Markov model	Five states in the model: no CD, CD but considered healthy, CD diagnosed but treatment failure (no GFD), CD diagnosed and on strict GFD, death. Cycle length 1 year. Life-years discounted at 3%	Lifetime	None	ICER of US$44,941 per life-year gained for screening, compared with no screening, using the EMA strategy. The results are highly sensitive to prevalence of CD: when prevalence is low, mass screening not justified because not cost-effective
Swigonski *et al.*[199] 2006	USA	To evaluate the cost-effectiveness of screening for CD among asymptomatic children with Down syndrome to prevent lymphoma	Screening for CD	No screening	Asymptomatic children with Down syndrome	Decision tree	Two strategies at decision node: screening or no screening for CD	Not reported	Utility of GFD and lymphoma (from Mein and Ladabaum[196])	Screening for CD among children with Down syndrome is not cost-effective. Screening is more costly and less effective than not screening, and it actually decreases quality of life. The results have not changed in sensitivity analyses. The intervention is never cost-effective at a US$50,000 threshold

continued

TABLE 62 Summary of economic models (*continued*)

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
Dorn and Matchar[200] 2008	USA	To evaluate the cost-effectiveness of strategies for diagnosing CD	Screening for CD (five diagnostic strategies)	All screening strategies compared in incremental analysis with next-best alternative	Adult population with Western European origins for which there was moderate suspicion for CD	Decision tree	Five strategies at decision node: tTG, tTG then OGD, tTG then IgA then OGD, tTG then HLA then OGD, OGD alone. Complications from biopsy were also modelled	Not reported	None	The use of OGD alone in all cases of suspected CD is too costly. The tTG-alone strategy is very cost-effective, highly sensitive and highly specific, but with low PPV and large numbers of false positives. When the prevalence of CD is low, patients with positive tTG should undergo OGD with biopsy to confirm CD. As the prevalence of CD increases, the cost of avoiding false-positive diagnoses via OGD with biopsy increases dramatically
Chang and Green[201] 2009	USA	To evaluate the cost of genetic testing before serological screening among relatives of patients with CD	Genetic screening (HLA) for CD	Serological screening with tTG	First- and second-degree relatives of patients with CD	Decision tree	Three diagnostic branches at decision node: tTG at time t0, tTG at time t0 and t1, HLA then tTG at time t0 and t1. All positive results will undertake biopsy to confirm diagnosis	None reported	None	Initial screening with tTG alone is the least costly, followed by repeat screening with tTG after some time; the most costly is HLA testing. The results are sensitive to costs of genetic test and prevalence of disease

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
Hershcovici *et al.*[202] 2010	USA	To evaluate the cost-effectiveness of mass screening for CD	Mass screening (serological tests followed by biopsy)	No screening (diagnosis based on symptoms alone)	Young adult general population at 18 years	Markov	Health states: no CD; CD undiagnosed, but with symptoms – IBS-like symptoms, IDA or other symptoms; CD undiagnosed without symptoms; CD diagnosed and adherence to a GFD; CD diagnosed without adherence to a GFD; death. Cycle length 1 year. Discount rate on costs and utilities: 3%	Lifetime		The screening strategy resulted in a gain of 0.0027 QALYs. The ICER of screening vs. the no-screening strategy was US$48,960 per QALY gained
Mohseninejad *et al.*[194] 2013	The Netherlands	Cost-effectiveness analysis of targeted screening for CD among IBS patients	Serological screening (tTG and IgA) and biopsy after positive serology	No screening	IBS patients in the Netherlands (aged 34 years)	Decision tree	Two decision options: no screening and screening. In the no-screening intervention, patients may have IBS or CD. The intervention arm classifies patients by test results first and not by prevalence. Test results, if positive, are confirmed by biopsy. Discount rates: 1.5% for utilities and 4% for costs, net present value calculated for all future costs	Lifetime	Utility on a GFD: 0.98 (based on SF-36 scores); utility of IBS: 0.76	Mass screening of young adults is cost-effective provided we assume that the utility of treated CD on a GFD is > 0.978. What drives the ICER: the time delay from symptom onset to diagnosis, the utility of adherence to a GFD, utility of treated CD and the prevalence of CD. Screening would be cost-effective if the time delay to diagnosis is > 6 years and utility of GFD adherence is > 0.978

continued

TABLE 62 Summary of economic models (*continued*)

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
Park *et al.*[203] 2013	USA	To determine the cost-effectiveness of universal serological screening to prevent non-traumatic hip and vertebral fractures among patients with CD	Universal serological screening (followed by biopsy)	Standard care (screening only symptomatic or at-risk patients)	Patients aged 12 years	Markov	Health states: CD, non-CD, fracture, disability, CD on GFD. Modelled males and females separately; different health states for the two interventions; 3% discount for costs and benefits, 1-year cycle	Lifetime	• Utility of hip fracture (0.9) based on Jönsson *et al.*[204] • Utility of vertebral fracture (0.9) based on Oleksik *et al.*[205]	Standard care dominates the intervention. The intervention costs 59.66 more for males and 54.99 more for females than standard care, and it is associated with a QALY loss of −0.005 for males and −0.01 for females. Results are robust and the DSA did not affect the ICER
Yang *et al.*[206] 2015	USA	Cost-effectiveness of routine duodenal biopsy for CD during endoscopy for gastro-oesophageal reflux	Performing a duodenal biopsy to detect CD during an OGD for GORD	No biopsy for patients undergoing OGD to detect CD	Patients with GORD (aged 40 years)	Decision tree	Two strategies considered (biopsy vs. non-biopsy): patients who already undertake an OGD for GORD could either be tested for CD (biopsy) or not tested. Adherence to GFD and whether or not symptoms of GORD improve are also modelled. Costs and effects discounted at 3%	Lifetime	Utilities included GORD (0.94) and CD on GFD (0.98)	Performing biopsy to detect CD among patients with GORD is not cost-effective. The model results were sensitive to the following variables: utility of GORD, prevalence of CD among refractory GORD patients, specificity of biopsy, cost of GFD and cost of PPI therapy
Broide *et al.*[207] 2016	USA	To determine the cost-effectiveness of routine duodenal biopsy to detect CD among patients with IDA	Performing a duodenal biopsy during an OGD among all patients with IDA, irrespective of serology CD result (even if CD results are negative)	Biopsy only in IDA patients with positive serology for CD	Adults with IDA, aged ≥ 45 years	Markov	Six health states in the model: (1) no CD; (2) CD but undiagnosed (i.e. considered healthy); (3) potential CD, defined as positive serology for CD; (4) CD under normal diet; (5) CD under strict GFD; and (6) death. Annual cycle length	Lifetime	• Utility of CD = 0.92 (based on published literature) • Utility of GFD = 0.99 (assumption)	The intervention is cost-effective and dominates the comparator as it costs less and results in more QALYs. The parameters that most affected the QALY gain results were the prevalence of CD among IDA patients, the utility of CD and the probability of identifying CD because of symptoms

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
NICE[193] 2015	UK	Which serological test is the most appropriate to diagnose CD and what patient group should be referred for screening?	• Individual or sequences of serological tests • Screening relatives of CD patients, patients with type 1 diabetes, and patients with autoimmune thyroid conditions	• Alternative testing and active case-finding strategies • No screening	Adults and children with symptoms suggestive of CD (the age of the cohort at baseline is an assumption, with 30 years being used for the adult population and 5 years used when the cohort begins in childhood)	Decision tree followed by Markov model	Health states of the Markov model: CD on GFD, CD no GFD, no CD, subfertility, osteoporosis, NHL, other cancers, death. Annual cycles. Health outcomes and costs are discounted at a rate of 3.5% in line with the NICE reference case	Lifetime	The health-care resource use data associated with symptoms of CD are based on a study by Violato *et al.*[50] Prescription costs are based on BNF chapters.[244] Resource use associated with long-term complications is based on published evidence specific to each of the complications considered (see NICE 2015, appendix G, table 7). Resource use associated with subfertility is estimated from the NICE guideline on fertility (CG156).[467] Resource use associated with osteoporosis was taken from Violato *et al.*[50] Endoscopy and biopsy costs were based on NHS reference costs	The diagnostic strategies that are cost-effective differ between adult and child populations. For adults, how effective strategies are is correlated with how sensitive they are. This is because false-negative results are associated with fewer QALY gains; therefore, the fewer false-negative results a strategy has, the more QALYs it accrues. Strategies with many false-positive results incur additional costs as a result of unnecessary biopsies. However, it is much more important in terms of cost-effectiveness not to miss people with CD than exposing some people to an unnecessary biopsy. For children, the specificity is more important because of the increased cost of biopsy in children. DSA results show that prevalence does affect results (if prevalence is > 17.5%, an IgA tTG assay alone becomes optimal)

continued

TABLE 62 Summary of economic models (*continued*)

Study	Country	Research question	Tests compared	Comparator	Population	Model type	Model structure	Time horizon	Relevant costs or QALYs	Conclusion
										Evaluation of active case-finding strategies found screening first-degree relatives of people with CD was cost-effective among adults and children, that screening people with type 1 diabetes was cost-effective among adults and potentially cost-effective among children, and that screening those with autoimmune thyroid disease was not cost-effective among adults or children

BNF, *British National Formulary*; CG, clinical guideline; DSA, deterministic sensitivity analysis; GFD, gluten-free diet; GORD, gastro-oesophageal reflux disease; PPI, proton-pump inhibitor; SBB, small bowel biopsy; SF-36, Short Form questionnaire-36 items.

Appendix 26 Age-stratified prevalence of coeliac disease-related complications

TABLE 63 Age-stratified prevalence of CD-related complications among CPRD Aurum patients with CD: mixed-gender cohort[a]

		Complication, *n* (%)		
Age category (years)[b]	*N*	NHL	Osteoporosis	IDA
0–9	3419	2 (0.06)	1 (0.03)	371 (10.85)
10–19	3803	0 (0)	19 (0.5)	544 (14.3)
20–29	5106	4 (0.09)	87 (1.7)	795 (15.57)
30–39	6005	8 (0.15)	207 (3.45)	1277 (21.27)
40–49	7417	28 (0.46)	594 (8.01)	2027 (27.33)
50–59	7778	49 (0.84)	1401 (18.01)	2116 (27.2)
60–69	7046	70 (1.37)	2199 (31.21)	2081 (29.53)
70–79	5153	60 (1.72)	2124 (41.22)	1957 (37.98)
80–89	2063	19 (1.46)	903 (43.77)	888 (43.04)
90–99	255	2 (1.41)	100 (39.22)	117 (45.88)

a Same prevalence at time of screening is assumed for newly diagnosed and undiagnosed CD.
b Patients may contribute to more than one age category because 20 years of data were used to estimate prevalence.

TABLE 64 Age-stratified prevalence of CD-related complications among CPRD Aurum patients with CD: men[a]

		Complication, *n* (%)		
Age category (years)[b]	*N*	NHL	Osteoporosis	IDA
0–9	1299	1 (0.08)	0 (0)	149 (11.47)
10–19	1417	1 (0.07)	5 (0.35)	132 (9.32)
20–29	1190	2 (0.17)	23 (1.93)	83 (6.97)
30–39	1603	2 (0.12)	59 (3.68)	137 (8.55)
40–49	2149	15 (0.7)	164 (7.63)	298 (13.87)
50–59	2652	27 (1.02)	314 (11.84)	568 (21.42)
60–69	2696	42 (1.56)	470 (17.43)	816 (30.27)
70–79	1993	36 (1.81)	458 (22.98)	772 (38.74)
80–89	778	15 (1.93)	208 (26.74)	340 (43.7)
90–99	79	1 (1.27)	23 (29.11)	36 (45.57)

a Same prevalence at time of screening is assumed for newly diagnosed and undiagnosed CD.
b Patients may contribute to more than one age category as 20 years of data were used to estimate prevalence.

TABLE 65 Age-stratified prevalence of CD-related complications among CPRD Aurum patients with CD: women[a]

		Complication, *n* (%)		
Age category (years)[b]	*N*	NHL	Osteoporosis	IDA
0–9	2120	1 (0.05)	1 (0.05)	222 (10.47)
10–19	2386	1 (0.04)	14 (0.59)	412 (17.27)
20–29	3916	2 (0.05)	64 (1.63)	712 (18.18)
30–39	4402	5 (0.11)	148 (3.36)	1140 (25.9)
40–49	5268	12 (0.23)	430 (8.16)	1729 (32.82)
50–59	5126	22 (0.43)	1087 (21.21)	1548 (30.2)
60–69	4350	41 (0.94)	1729 (39.75)	1265 (29.08)
70–79	3160	42 (1.33)	1666 (52.72)	1185 (37.5)
80–89	1285	19 (1.48)	695 (54.09)	548 (42.65)
90–99	176	3 (1.7)	77 (43.75)	81 (46.02)

a Same prevalence at time of screening is assumed for newly diagnosed and undiagnosed CD.
b Patients may contribute to more than one age category because 20 years of data were used to estimate prevalence.

Appendix 27 Fracture rates and costs of osteoporosis

TABLE 66 Fracture rate by age at the sites, sourced from Curtis *et al.*[226]

Age range (years)	Hip fracture rate per 10,000 person-years	Number of cases	Vertebral fracture rate per 10,000 person-years	Number of cases	Wrist (carpus) fracture rate per 10,000 person-years	Number of cases
18–49	0.5	1520	1.5	5027	20.7	65,244
≥ 50	19.6	52,609	7.1	19,232	12.5	32,983

TABLE 67 Cost calculations: osteoporosis

	Fracture		
Parameter	Hip	Vertebral	Wrist
Probability of fracture among those aged ≥ 50 years	0.00196	0.00071	0.00125
Cost (£)	16,302 × 1.17 = 19,073	479 × 1.80 = 862.20	468 × 1.80 = 842.40
Total cost (£)	37.38	0.61	1.05
Overall cost	39.04 (SE 0.27)[a]		

a Using gamma distributions moment-matched to cost of hip, vertebral and wrist fractures where SE of cost is assumed one-tenth of the mean.

Appendix 28 Utilities

TABLE 68 The EQ-5D index UK population norms

Age group (years)	EQ-5D index population norms
18–24	0.934
25–34	0.922
35–44	0.905
45–54	0.849
55–64	0.804
65–74	0.785
≥ 75	0.734

Note
Values sourced from Janssen and Szende.[230]

TABLE 69 Utility calculations: osteoporosis

Parameter	Hip	Vertebral	Wrist
Probability of fracture among those aged ≥ 50 years	0.00196	0.00071	0.00125
Disutility	0.817 – 0.59 = 0.227	0.817 – 0.55 = 0.267	0.817 – 0.78 = 0.037
Total disutility	0.0004	0.000026	0.0003
Overall disutility	0.0004 (SE 0.00067)[a]		

a Uncertainty was modelled by moment-matching beta distributions to the hip, vertebral and wrist fracture disutilities, with the SE for each set to one-tenth of their means.

Appendix 29 Application of UK National Screening Committee criteria to a hypothetical adult coeliac disease screening programme

TABLE 70 Application of UK National Screening Committee Criteria to a hypothetical adult CD screening programme

UK National Screening Committee criteria	Application to hypothetical adult CD screening programme
Condition	
1. Must be important health problem judged on frequency/severity	CD is common, has severe impact on health and is underdiagnosed
2. Primary prevention interventions should have been implemented	There are no primary prevention interventions for CD
3. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications	Not applicable
Test	
4. Should be a simple, safe, precise and validated screening test	IgA tTG fulfils these criteria
5. Distribution of test values in the target population should be known and a suitable cut-off level defined and agreed	The distribution of test values is known, but the most appropriate threshold for screening has not been identified – this may be lower than for diagnosis to increase sensitivity
6. Test should be acceptable to the target population	The test is a simple blood test and so likely to be acceptable
7. Agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals	There are various options for the workup of those with a positive test that would need further work – this could include combinations of additional serological testing, genetic testing and biopsy
8. If the test is for a particular mutation or set of genetic variants, the method for their selection and the means through which these will be kept under review in the programme should be clearly set out	Not applicable (unless HLA is recommended as part of the further workup of those testing positive)
Intervention	
9. Should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care	Gluten-free diet is an effective intervention and starting this as early has possible has beneficial effects
10. There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered	This is fairly straightforward for CD as the only treatment is a gluten-free diet, which is recommended for anyone with CD

continued

TABLE 70 Application of UK National Screening Committee Criteria to a hypothetical adult CD screening programme (*continued*)

UK National Screening Committee criteria	Application to hypothetical adult CD screening programme
Screening programme	
11. Should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity	Not currently available
12. Should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public	Screening programme is likely to be acceptable, but further evidence on this may be required
13. Benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	Our economic analysis provides evidence for this
14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost–benefit and/or cost-effectiveness analyses and have regard to the effective use of available resources	Our economic analysis suggests that screening may be cost-effective

Notes
Dark blue: criteria that are fulfilled; light blue: uncertain, further evidence required; orange: criteria not fulfilled.
The criteria have been reproduced from the UK National Screening Committee.[284] Contains public sector information licensed under the Open Government Licence v3.0.

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HTA
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