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Screening for celiac disease in the general population and in high-risk groups

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Abstract

Background: Celiac disease (CD) occurs in approximately 1% of the Western population. It is a lifelong disorder that is associated with impaired quality of life (QOL) and an excessive risk of comorbidity and death.

Objectives: To review the literature on screening for CD in relation to the current World Health Organization (WHO) criteria for mass screening.

Methods: We performed a *PubMed* search to identify indexed papers on CD screening with a publication date from 1900 until 1 June 2014. When we deemed an abstract relevant, we read the corresponding paper in detail.

Results: CD fulfills several WHO criteria for mass screening (high prevalence, available treatment and difficult clinical detection), but it has not yet been established that treatment of asymptomatic CD may reduce the excessive risk of severe complications, leading to higher QOL nor that it is cost-effective.

Conclusions: Current evidence is not sufficient to support mass screening for CD, but active case-finding may be appropriate, as we recognize that most patients with CD will still be missed by this strategy. Although proof of benefit is still lacking, screening for CD may be appropriate in high-risk groups.

Keywords

Celiac disease, gluten, gluten-free diet, review, screening, prevention, risk, quality of life, World Health Organization

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Introduction

Celiac disease (CD) occurs in about 1% of the Western population.[1,2] A recent multinational study in Europe found big differences in CD prevalence, with the lowest prevalence (0.3%) in Germany and the highest in Finland (2.4%), despite using common criteria for CD diagnosis.[3]

The prevalence of CD seems to be increasing.[4–7] A true increase in prevalence is probably one explanation, but other factors may also have contributed. Increased awareness of the complications of CD (including excessive mortality),[8] in combination with the advent of serological tests with high sensitivity and specificity[9–12] mean that active case finding in CD has increased dramatically in the last decades. Among groups where screening is now becoming more and more common are: first-degree relatives and patients with Type 1 diabetes.[13,14]

The main objective of this paper was to review the literature on screening for CD, in relation to the established criteria for mass screening that was established by the World Health Organization (WHO).

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Methods

This project was part of a wider effort, initiated by the British Society of Gastroenterology (BSG) and the Oslo group,[15] to establish recommendations for the care of patients with CD. Authors JFL and DSS coordinated that overall effort. As part of a major review on the clinical management of CD,[14] we had briefly described the role of screening for CD. In the current paper, we expand that discussion and look at the background of screening, and the pros and cons for CD screening; including the impact that such detection of CD will have on dietary adherence, outcome and quality of life.

The working group for the present paper was made up of seven authors from six different countries (two from the UK and one author each from Sweden, Finland, Italy, Argentina and the US). Four authors (JFL, TC, KK and JAM) carried out the literature searches, the data collection and took the main responsibility for the writing of the paper. JB, FZ and DS provided important feedback, and contributed to crucial revision of the paper. JFL wrote the first draft.

The recommendations of this paper were based on a systematic literature review in the PubMed database, for the time period from 1900 until 1 June 2014 (search criteria are listed in the appendix). We initially carried out seven PubMed searches (Appendix) but given the large number of hits for three of these, we limited our literature review to the remaining four terms, combined with both the UK and US spelling of celiac disease (search terms: definition, cultural, diagnostic delay, undiagnosed, and complication or comorbidity). The parts of this paper dealing with CD prevalence, treatment (i.e. gluten-free diet (GFD)) and serological sensitivity/specificity were based on the authors' personal knowledge. Finally, CD screening in general was discussed within the author group.

Results

The WHO stipulates a number of criteria that need to be met, to support mass screening (Table 1). While it is evident that CD readily meets many of these criteria, others have not yet been met. For example, CD is more prevalent than some disorders for which there is already mass screening (e.g. phenylketonuria (PKU)), but it is unclear whether early detection of CD would have a positive societal impact. In contrast, detecting a child with PKU will allow the prevention of devastating consequences for the child's development and quality of life (QOL).

Prevalence of CD: "That the disease is common and well defined"

In much of the Western world, CD affects about 1% of the population, but the prevalence varies between countries (e.g. 0.3% in Germany,[3] 0.7% in Italy,[3] 0.7–0.8%

Table 1. Summary of WHO criteria

WHO criteria	Valid in celiac disease	Comment
The disease is common and well defined	++	There is agreement that the disease occurs in about 1% or more of the Western population; however, disease criteria have been debated.
Screening tests are simple, safe and accurate	++	Screening tests with tissue transglutaminase have high sensitivity and specificity, but the PPV is well below 100%; however, when combined with sequential endomysial antibody testing, the PPV increases.
The screening test should be culturally acceptable	+++	Only very rarely is screening not culturally accepted.
Treatment is available	+++	A GFD is beneficial for both symptoms and mucosal injury, but may not protect against many future complications of CD.
Clinical detection is difficult	+++	Symptoms and signs vary, and some individuals with CD are asymptomatic. Most people with CD remain undetected.
If undiagnosed and untreated, the disease will lead to severe complications	+	Symptomatic patients will most often be relieved of symptoms. It is less clear if asymptomatic patients will benefit from clinical diagnosis and treatment with a GFD. It is not known if asymptomatic individuals are at risk of severe complications.
Testing and treatment is cost-effective	+	There is little research in this field. Existing research is often based on the assumption that CD goes undiagnosed for many years. With increasing awareness of CD, diagnostic delay is likely to have decreased in recent years.

CD: celiac disease; GFD: gluten-free diet; PPV: positive predictive value; WHO: world health organization.

in the US[16,17] and 1.8% in Sweden[2]). There are reports of even higher prevalence in certain calendar- and age-specific population-strata in Sweden.[18]

The proportion of individuals with CD whom have received a physician-assigned diagnosis of CD also varies (e.g. 25% in Finland and 6% in Italy),[3] probably reflecting the general awareness of CD in each country. The ratio between diagnosed and undiagnosed CD has implications for screening, because with a large proportion of undiagnosed CD, the arguments for screening become stronger. Despite the slightly varying prevalence of CD, it is one of the most common lifelong diseases in any Western country (especially in children). While the prevalence of CD may be lower in some non-Western countries,[19,20] there are also reports of extremely high prevalences in others.[21] We concluded that this WHO condition is fulfilled.

There is currently an ongoing debate on how to define CD. Our research group recently published a paper on the definitions of CD, where CD was defined as "a chronic, small intestinal immune-mediated enteropathy, precipitated by exposure to dietary gluten in genetically-predisposed individuals."[15] The related non-celiac gluten sentivitity[15,22,23] was defined as: "one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded."[15] The definition of CD has important implications for CD screening, because so far, most research on complications and QOL have been performed in individuals with biopsy-verified CD, and that data cannot automatically be extrapolated to non-celiac gluten sensitivity. The risk of complications may also vary with the underlying histopathology in CD.[24]

Serology sensitivity and specificity: "That screening tests are simple, safe and accurate"

The WHO stipulates that for mass screening to be an option, screening tests with high sensitivity, specificity,[25] positive predictive value (PPV) and negative predictive value (NPV) must be available. For any of the available tests, a most important aspect is that the testing should be carried out when the patient is on a gluten-containing diet. It is, therefore, of crucial importance that the patient remains on a normal diet throughout the investigation for CD, and our discussion assumes this will be so.

So-called antigliadin antibodies used in the 1980s and 1990s have low PPV, even in high-risk groups; and therefore, they have largely been replaced by the more specific endomysium (EMA) and tissue transglutaminase antibodies (TTG). The introduction of endomysium antibodies was initially promising, because their sensitivity and specificity seemed to be at least 90–95%; but over time, issues regarding inter-observer reliance/interpretability and cost, have limited its use as the first-line screening tool for CD. Though TTG antibodies can also be elevated in non-CD diseases such as liver disease,[26] gastrointestinal infections[27] and certain heart diseases;[28,29] TTG, like EMA, offers high sensitivity and specificity.[30]

One further test recently gained some popularity: This is for deamidated gliadin peptide antibodies (DGP); however, one meta-analysis found that TTG performs better than DGP.[31] TTG is therefore often used for screening of high-risk groups, but it has also been used in large-scale screening projects of the general population, including that of a multi-national European study encompassing more than 29,000 individuals.[3] In this European multi-center study, 75% ($n = 292/391$) of individuals with positive TTG were positive for EMA, but only 2.6% of those had borderline TTG values ($n = 10/384$).[3] In the 147 individuals with both positive EMA and positive/borderline TTG, 100 had an enteropathy that was typical of CD, equaling 68%.[3] When Hopper et al.[32] screened a population of 2000 individuals undergoing endoscopy for various indications, the PPV for CD (as defined by villous atrophy) in TTG+ individuals was 28–29%; but with a much higher figure reported in a general population study by Katz et al.,[33] as well as by Sugai et al.[34] Even a PPV of around 30% compares favorably with the PPV of guaiac fecal occult blood (FOB) testing for colorectal cancer (a test already accepted for screening in a number of countries), for example; however, in the case of FOB screening, confirmatory testing is recommended (in the case of CD in adults, through a small intestinal biopsy).[14]

One further aspect to consider in the use of TTG is that when determining TTG (TG2 antibodies) by enzyme-linked immunosorbent assay (ELISA), it is important to bear in mind that the performance of commercial ELISA TTG assays may vary depending on the quality of the TTG antigen.[35] The method of extraction, the purity of TTG and the production and processing of recombinant antigen may all have an effect on the test results.[35–37] Furthermore, as TTG can exist in two divergent conformations (open extended or closed), dependent on the activity of the enzyme,[38] this also will influence the performance of the assay, with the open TTG being the superior antigen.[39] For the above-mentioned reasons, the different commercial TTG-ELISA tests can yield differing numbers of false-negative or false-positive results. Sequential strategies may also be used, to increase the PPV.[2,40]

When screening may be insufficient. Under certain circumstances, a negative screening test cannot rule out CD.

This will occur when the pre-test probability of CD is elevated. For instance, individuals with severe gastrointestinal symptoms, especially those with a family history of CD, should undergo small intestinal biopsy, even in the absence of elevated antibodies.[41] Similar arguments apply to children with growth failure and individuals with severe gastrointestinal symptoms at the same time as another autoimmune disease, such as Type 1 diabetes, thyroid disease or Addison's disease. Although IgG-based serology tests have been developed in recent years, a combination of IgA deficiency and gastrointestinal symptoms may also constitute an indication for biopsy. One way to effectively exclude CD in IgA-deficient individuals is to perform a human leukocyte antigen (HLA)-test first, thereby ruling out CD in those whom are negative for DQ2 or DQ8. Differential diagnoses such as common variable immunodeficiency (CVID) or severe *Giardia* should also be considered.

Screening is culturally acceptable

A third WHO criterion is that "a screening test should be culturally acceptable." There are areas in the world[42] where blood testing may not be culturally acceptable, but in the majority of countries (including those where earlier research shows a high prevalence of CD), blood testing is culturally accepted.

The GFD: "That a treatment is available."

This condition is clearly fulfilled in CD. Use of a GFD is an effective treatment for CD; and in symptomatic patients, the benefits of dietary treatment are well established, as it has been shown to decrease clinical symptoms, as well as to reduce the excess risk of complications.[43–45]

Nevertheless, the advantages of dietary treatment in screening-detected but apparently asymptomatic individuals remain doubtful, and it is by no means settled that a GFD results in similar health gains;[46–51] however, it is important to note that many screening-detected CD patients are not truly asymptomatic at diagnosis; and may, once on a GFD, recognize that they had suffered from CD-related symptoms before the diagnosis. It is suggested that many undiagnosed celiac patients accept a state of chronic vague ill health as a normal condition, but are able to recognize this only after they have been placed on a GFD.[47,52–54]

A recent randomized study also shows that apparently asymptomatic EMA-positive subjects seem to benefit from their serological screening and subsequent GFD,[55] thereby supporting earlier evidence from Dickey et al.;[56] however, some authors have suggested that EMA positivity in individuals with normal mucosa constitutes a separate entity (potential CD), different from CD.[57]

A strict GFD sets major limitations on daily life and it is expensive and difficult to maintain.[58,59] Furthermore, removal of gluten from baked products makes them less palatable than comparable products in the normal diet. Due to these unpleasant aspects, adherence to a GFD often remains inadequate.[60] Individuals who are found through screening programs to have CD may feel themselves healthy and they do not expect to gain health on a treatment similar to those who were detected due to having symptoms. Consequently, screening-detected subjects may be even less willing to adhere to a strict GFD.[53,61,62] The possible non-adherence to a GFD is an essential issue, when weighing the harms and benefits of CD screening; as a low rate of adherence would abolish any advantages of performing that screening. It is important in this regard to recognize that good dietary adherence can be achieved in screening-detected CD patients (adherence rates of 85% in the symptom-detected CD patients and 79–91% in the screening-detected ones),[53,63] even after long-term treatment;[52,64] however, there is evidence to suggest that dietary lapses could be more common in the initially asymptomatic screening-detected patients than in the symptomatic ones.[53] Furthermore, patients suffering from Type 1 diabetes mellitus and found to have CD by risk-group screening may evince lower dietary adherence rates than are reported in screening studies in general (40–63%).[65–67]

When prescribing a GFD to a healthy screening-detected patient, one should remember that a GFD is not nutritionally optimal and may have adverse consequences. GFD may potentially expose individuals to high sugar, and low fiber and mineral intake;[68,69] which might cause different long-term negative health consequences, such as constipation.[70] In addition, there is concern that patients might gain undesirable weight while on a GFD.[71,72] Altogether, it would thus be essential to evaluate the consequences of GFD treatment before any screening programs for the disease are instituted.

Diagnostic delay: "That clinical detection is difficult"

Typically, CD is characterized by diarrhea, malabsorption and failure to thrive in childhood, although during the last 2 decades, the age of diagnosis has shifted upward and many patients exhibit only minor symptoms.[73–75] Due to the inconsistency of their symptoms, a substantial proportion of celiac patients have a previous diagnosis of irritable bowel syndrome (IBS).[76,77] Unfortunately, these symptoms do not predict CD in general population studies.[2,33,78,79]

Furthermore, increasing numbers of CD patients are diagnosed because of extraintestinal symptoms or by screening of at-risk groups.[73,74] Probably due to the vague nature of presenting symptoms, the delay from first symptoms to CD diagnosis has been reported to be unacceptably long, at between 5–10 years for many persons;[73,80–85] and so the need for earlier diagnosis, even by mass screening, has been advocated.

Untreated disease leads to complications: ''That if undiagnosed and untreated, the disease will lead to severe complications''

The WHO stipulates that prevention of complications shall follow upon disease detection, if mass screening is implemented. This statement is conditional on two facts:

- That undiagnosed disease confers complications; and
- That these complications can be prevented by a treatment; in this case, a GFD.

Given the importance of genetic factors in the etiology of CD, it may be assumed that comorbidity linked to underlying shared risk factors cannot be modified by diagnosing CD and introducing a GFD.

It seems clear that the majority of gastrointestinal symptoms in CD are alleviated after the introduction of a GFD, but the evidence is less clear about whether most complications are influenced by a GFD. Weaknesses of previous research in this area include: lack of strict evaluation of GFD, low study power, short follow-up, a difficulty in disentangling the effects of age at diagnosis and the duration of gluten exposure that will likely both be linked to early diagnosis.

It should be noted that duration of CD is not equal to diagnostic delay. In the recent 'Proconsul' study, complications in CD were associated with a short diagnostic delay,[86] but it cannot be ruled out that earlier celiac diagnosis was prompted by the symptoms and signs from the celiac complication.

Morbidity and mortality in undiagnosed CD

Mortality. A number of studies examine mortality in undiagnosed CD.[6,51,87–90] Two of these have shown excess mortality.[6,90] Of particular interest is the study by Rubio-Tapia et al.,[6] which is the only study with extensive follow-up duration. That study found an almost 4-fold increased risk of death in young men with CD+ serology, but the confidence intervals (CI) were wide (95% CI = 2.0–7.5), the number of participants with CD was low ($n = 14$), and the population studied was restricted (military recruits); so the results may not be generalizable.[6] It is also not clear how many of these individuals would have been diagnosed by applying modern aggressive case-finding for CD,[91] as many individuals diagnosed in the screening studies have a history of CD-associated symptoms.[47] Other larger-scale studies show no increased risk of death in undiagnosed CD (*n* of screened adults: 16,847;[89] 7,527[87] and 6,987[88]).

Autoimmunity. Studies on undiagnosed CD and autoimmune disease are difficult to carry out, because patients with autoimmune disease are often screened for CD and because the onset of autoimmune disease is often gradual (in contrast to mortality; but also to some extent, malignancy). As far as we know, none of the studies looking at undiagnosed CD and mortality look at the development of autoimmune disease.[6,51,87–90]

Cosnes et al.[92] investigated 924 patients with CD. While they concluded that the GFD had a protective effect against autoimmunity, this effect was weak, because it did not remain statistically significant when the authors adjusted for the other co-variates in their multivariate analyses ($p = 0.07$). The Cosnes et al.[92] study also found that a *late* diagnosis of CD decreased the risk of autoimmune disease. Finally, two Italian studies suggest that GFD may decrease the prevalence of thyroid autoantibodies,[93,94] but whether it protects against hypo- or hyper-thyroidism is still unclear.

We may however want to consider the effects of a GFD not only upon the cumulative incidence of autoimmune disease in those with CD, but also upon the control of disease in individuals whom already have an autoimmune disease other than CD. Diagnostic delay of CD is common in Type 1 diabetes[95] and the long-term consequences of this are unknown; however, recent Swedish data indicate that long-term CD is associated with excess morbidity in Type 1 diabetes.[96–98] Hansen et al.[99] screened children with Type 1 diabetes, but did not see an improvement of HbA1C in diabetes patients whom were detected with CD and then recommended a GFD; however, a British study of adults with Type 1 diabetes found that patients with undiagnosed CD had worse HbA1C than controls (8.2 versus 7.5, respectively; $p = 0.05$) at baseline; but when after 1 year the authors compared HbA1C values, there was no difference between those adhering to a GFD and those with poor adherence.[100]

Malignancy. A recent meta-analysis even suggests that the overall malignancy risk in diagnosed CD was not elevated, compared to that of general population-based controls;[101] but that individual cancers, such as lymphoproliferative cancer and gastrointestinal cancers,[102,103] may still be positively associated with CD. One reason for a seemingly neutral association between diagnosed CD and the risk of overall cancer

(or a very limited risk increase) is that high relative risks for less common cancers (lymphomas) may be compensated for by lower relative risks for common cancers, such as breast cancer.[104,105]

We know of three studies so far that explore cancer risk in undiagnosed CD, none of which found any increase in overall cancer, but their study power was limited.[89,106,107] In addition to these, there are at least another two case control studies specifically of lymphoma, which show an excess risk in CD. Catassi et al.[108] find a 3.1-fold excess of non-Hodgkin lymphoma (NHL) among Italian individuals with undiagnosed CD and 16.9-fold for gut lymphoma. The latter of these figures closely mirrors the odds ratio of 15.7 for the occurrence of gut lymphoma in undetected CD, seen by Johnston and Watson[109] in Northern Ireland; however, as with mortality, one must consider the risk in those with diagnosed disease, because the risk of NHL remains greater in diagnosed disease, at about 4–6 fold[24,103,110] (and that of small bowel lymphoma (SBL) may be even higher in this group);[111] which is again a substantial societal benefit in the reduction of cancer occurrence or death from mass screening for CD that seems unlikely.

Considering that the overall risk of malignancy in CD does not seem to become increased more than marginally,[101] most interest with regards to the potentially protective effect of GFD focuses on lymphoproliferative malignancy. That earlier research on undiagnosed CD failed to show an association with malignancy, including lymphoproliferative malignancy, argues against GFD playing a major role. At the same time, it should be noted that most of the earlier studies were underpowered to examine the relationship between GFD and lymphoproliferative malignancy (*n* of CD patients with lymphoma or non-Hodgkin lymphoma: 9,[112] 9[44] and 9[103]). In an effort to examine the role of GFD, Olen et al.[113] reviewed patient charts (blinded to CD status) of 59 patients with both CD and lymphoma, as well as 137 CD patients *without* lymphoma. This nested case-control study was still underpowered to confirm a suspected relationship between poor dietary compliance and future lymphoma (OR = 1.83; 95%CI = 0.78–4.31).[113]

Current data implies that there is a protective effect of a GFD against lymphoma, although that has not yet been comprehensively proven.

Pregnancy and fertility. An adverse pregnancy outcome in maternal *undiagnosed* CD is now confirmed by a number of studies,[114–116] including two recent papers that both find increased risk estimates for preterm birth in undiagnosed CD (Sweden: 1.71[117] and Denmark: 1.33[116]), but not in diagnosed CD. This association strongly argues that a CD diagnosis and a GFD introduced before pregnancy does influence pregnancy outcome; however, as both studies were of clinically-diagnosed cases, they do not clearly demonstrate a benefit to screening for asymptomatic ones.

The fact that undiagnosed CD has a negative effect on birth outcome cannot automatically be translated into an effect on fertility. The largest screening study for CD in subfertile/infertile couples so far found no association with CD;[118] and the two largest cohort studies to this date[119,120] found that overall fertility in CD is similar to that of general population controls, even though the Swedish study found a fertility decrease in the last 2 years before diagnosis, followed by catch-up fecundity after diagnosis.[119] It cannot be ruled out that the decrease in fertility just before diagnosis that was seen in that paper was due to the undiagnosed CD,[119] but it might also be due to other comorbidities that led to testing for CD, or that women postpone pregnancy when they undergo extensive medical investigations.

Advantages of undiagnosed CD. Although we do not argue that patients with symptomatic CD should remain undiagnosed, several papers suggest that the prevalence of hypertension,[121] hypercholesterolemia[121,122] and obesity[123] is lower in undiagnosed CD than in the general population,[121] potentially protecting against cardiovascular disease. In fact, some authors have argued that screening-detected children without symptoms should not always be treated with GFD.[52]

The largest study on diagnosed CD and cardiovascular disease found a small but statistically significant increase in the relative risk for both incident ischemic heart disease and death from ischemic heart disease;[124] however, such a risk increase does translate into a substantial absolute risk, considering that cardiovascular disease is common (in individuals with CD aged 60+ years, the excess risk was equivalent to 20 myocardial infarctions per 1000 person-years).[124]

QOL aspects of screening for CD

In symptomatic CD, the GFD results in rapid recovery from symptoms, paralleled with improvement in QOL[46,53,125–127] (Table 2); however, screening-detected CD patients may have considered themselves healthy before the diagnosis, and now the stigma of a chronic disorder[128] and need of major dietary restrictions may potentially even increase their self-perceived burden of illness and impair their QOL.[129–131]

Prospective studies on QOL in CD patients detected by screening of at-risk groups or in populations in general are limited (Table 2). According to these studies, QOL in screening-detected CD patients at or before diagnosis, especially in those whom are asymptomatic,

Table 2. QoL studies in screen-detected coeliac patients

Reference	Country	Study design	Screen-detected patients (*n* asymptomatic)	QoL instrument	Main finding
Mustalahti et al.[125] 2002	Finland	Prospective	19 (14)	PGWB	At diagnosis, QoL similar to controls; QoL improved significantly after 1 year of GFD.
Johnston et al.[46] 2004	UK	Prospective[b]	14 (ND)	SF-36	At diagnosis, QoL similar to controls; no change after 1 year GFD.
Viljamaa et al.[64] 2005	Finland	Cross-sectional	53 (32)	PGWB, SF-36	After long-term GFD, QoL was comparable to controls.
Korponay-Szabo et al.[47] 2007[c]	Hungary	Prospective[b]	32 (5)	Generic child health questionnaire	Global general health, body pain, general health perceptions, parental emotional impact were lower than in controls; QoL improved after 1 year of a GFD.
Whitaker et al.[48] 2009	UK	Cross-sectional	51 (19)	Self-made questionnaire	One-quarter of the asymptomatic screen-detected patients regretted being diagnosed.
Van Koppen et al.[52] 2009[c]	Netherlands	Prospective[b]	32 (20)	TNO-AZL[a] DUX 25[a] CDDUX[a]	Social functioning, problem behavior, anxiety, positive mood, liveliness affected in cases, versus control population. Improvement upon GFD.
Nachman et al.[126] 2009	Argentina	Prospective	(8)	SF-36	At diagnosis, QoL similar to controls; after 3 months of GFD, no change.
Ukkola et al.[53] 2011	Finland	Prospective	146 (23)	PGWB	In all groups, at diagnosis QoL was lower than in controls; QoL improved after 1 year of a GFD. In asymptomatic group, QoL similar to controls at diagnosis; no change after 1 year of GFD.
Nordyke et al.[50] 2011[c]	Sweden	Cross-sectional[b]	148	EQ-5D	Before diagnosis, QoL in screen-detected CD similar to controls.
Nordyke et al.[158] 2013[c]	Sweden	Prospective	103	EQ-5D	Screen-detected cases with unrecognized CD experienced similar QoL at diagnosis. On diet, boys report less pain.
Myleus et al.[159] 2014[c]	Sweden	Cross-sectional	238	Kidscreen	Comparable HR QoL as their peers.
Kurppa et al.[55] 2014	Finland	Randomizedand prospective	40	PGWB SF36 VAS	Anxiety alleviated and perception of health improved in favor of GFD, but social functioning reduced in favor of gluten consumption.

[a]QoL scales: For an explanation, see the original paper by Van Koppen et al.[52]
[b]Detected by mass-screening (other studies include patients detected by risk-group screening).
[c]Study based on children and/or adolescents (All other studies were based on adults).
CD-Dux: celiac disease dux; GFD: gluten free diet; HR: hazard ratio; ND: no data; PGWB: psychological general well-being; QoL: quality of life; SF-36; Short Form-36; TNO-AZL: The Netherlands Organisation for Applied Scientific Research Academic Medical Centre; VAS: visual analogue scale.

is often similar to[46,50,53,125,126] or lower[47,52,53] than that found in control populations. In screening-detected patients, GFD treatment does not necessarily result in improvement of QOL,[46,53,126] but some studies imply that the diet may also have a positive impact on the health and well-being of these patients.[47,52,53,125] Still, data suggest that screening-detected patients without symptoms may experience the diagnosis of CD more negatively than the patients with symptoms.[48,53] This would suggest that early detection of CD by mass screening in a healthy adult population would not unequivocally result in a self-perceived health gain. Furthermore, data on long-term treatment in screening-detected patients is scarce.[52,64] These issues call for comprehensive studies before implementation of large-scale CD screening programs.

Cost-benefit of screening: ''That testing and treatment is cost-effective''

As has been outlined above, the likely benefit or even the potential harm to undetected coeliac patients from screening detection is as yet poorly defined. In addition, symptomatic undiagnosed CD and diagnosed CD are both likely to confer increased costs to the individual patient and to society, but these costs are shared differently in different countries. Determining whether screening and detection of asymptomatic CD will lead to health gains at an acceptable cost, or even to economic benefits, is therefore extremely difficult; however, a number of studies have been conducted in this area. Some of these consider only the costs of detecting a new case by varying screening strategies, or apply only to specific high-risk groups, and there are very few that have attempted to model both costs and health benefits, to determine the cost of gaining a quality-adjusted life year (QALY). Only three of these refer to general population screening.

In a UK context, perhaps the most influential of these papers to date is the Health Technology Assessment (HTA) sponsored study, by Dretzke et al.[132] (the only such study that is considered in the development of the current UK national guidelines; and one that is specifically looking at newly-diagnosed Type I diabetic children). This study finds that serological testing, followed by confirmatory biopsy and then treatment with GFD, provides additional QALYs at an incremental cost of between £12,250 and £20,160, when performed in children with newly-diagnosed Type 1 diabetes. To derive these estimates, the authors assumed, among other things, that untreated asymptomatic CD would cause the loss of 4 years of life, and reduce QOL from the 88% optimal assumed baseline for treated disease, to 82% of optimal.

Another prominent analysis by Hershcovici et al.[133] examines the cost-effectiveness of mass screening. This paper found that the cost for each QALY gained through mass CD screening is about US$49,000 (Table 3);[133] however, it is important to note that this cost, and the conclusion that mass screening in young adults is cost-effective, is again based on a number of assumptions. The authors of the Hershcovici et al.[133] paper assume that the standardized mortality ratio (SMR) is 1.6 in patients with symptoms that are 'undiagnosed CD', and 1.1 in 'diagnosed' patients on a GFD; however, most studies on mortality in diagnosed CD find relative risks of deaths of around 1.3–1.4[8,104] (and in a Swedish study,[8] it was estimated that 83% of patients adhere to their diet). Hence, with a smaller gap between the mortality risk estimates between diagnosed and undiagnosed celiac patients, mass screening may not be cost-effective. This is well illustrated by the study by Shamir et al.[134] (Table 3), which though finding on an assumption of a SMR of 1.6 for undetected disease that screening is cost effective, shows in a sensitivity analysis that if the SMR fell to 1.3, then the cost per QALY rises to over US$100,000.

Cost-effectiveness analyses are also dependent on the degree of adherence to a GFD, and where Hershcovici et al.[133] assume a dietary adherence of 80% in patients with symptomatic CD, others find the lowest dietary adherence in screening-detected asymptomatic patients.[49] Finally, cost-effectiveness is dependent on

Table 3. Cost effectiveness of mass screening for celiac disease

	Shamir et al.[134]	Hershcovici et al.[133]
Utility of life with untreated asymptomatic CD	100%	IBS 76% Iron deficiency anemia 73% All other presentations 100%
Utility of life on GFD	100%	98%
SMR for untreated asymptomatic CD	1.6	All assumed symptomatic. With SMR 1.6
SMR in GFD	1.1	1.1
Sensitivity of screening	85%	IgA TTG 95% IgG TTG 98.7%
Prevalence of CD	0.5%	0.9%
Specificity of screening	90% TTG 95% EMA	IgA TTG 98% IgG TTG 98.6%
Costs of screening from	2004 Medicare fees	2004 Medicare fees
Cost of GFD	Not considered	Not considered

EMA: endomysial antibodies; GFD: gluten-free diet; IBS: irritable bowel syndrome; Ig: immunoglobulin (antibodies); SMR: Standardized Mortality Ratio; TTG: tissue transglutaminase antibodies.

the duration of symptoms before diagnosis. Hershcovici et al.[133] report that mass screening would be effective, if the diagnostic delay was 6 years or more. With increased awareness of CD, the diagnostic delay is likely to decrease. At present, some studies suggest that the delay is ≥ 6 years,[80,85] but others suggest that it is less (4.9 years).[135]

Finally, Park et al.[136] recently compared two different strategies to prevent bone loss and fractures in patients with undiagnosed or subclinical CD. Their study found that symptomatic at-risk screening was more cost-effective than universal serological screening. Though again, the assumptions of their base model can be challenged, they find that screening of symptomatic and high-risk subjects is the dominant strategy, when compared to universal screening, producing greater QOL gains at a lower cost. Furthermore, this strategy remains the more cost-effective option when testing the sensitivity of the model to variation in their assumptions.

We conclude that more data on the cost-effectiveness of mass screening for CD in the general population is needed.

When and how often should we screen? It should be clear to all that for so common a disease as CD, and with so successful a therapy as GFD, any patient with symptoms that might be due to CD should be tested; however, in this paper we are primarily concerned with asymptomatic CD. For these people, as should be clear from the forgoing, we cannot point to a definite benefit from the detection of CD (neither in the reduction of symptoms, since they have by definition none, nor an increase in the quality or the quantity of life). Furthermore, unlike in congenital diseases such as congenital hypothyroidism, where screening once is enough to rule out disease, CD can start at any age, so having one negative CD serology test does not rule out future CD.

With regard to the second of these issues, there is at least one CD screening method with an exceptionally high NPV: HLA-screening. Patients with a negative HLA will not develop CD, so one strategy to avoid repeated CD screening is to first perform an HLA test. One drawback of HLA screening is its extremely low PPV (1 in 25 DQ2-DQ8 individuals will develop CD, i.e. the PPV is around 4%), while giving the patient and his/her physician the impression that the patient is CD+.

No simple work-around exists, however, for the lack of clear evidence for the benefit of CD detection by screening; however, it is not unreasonable to assume that there is a marginal benefit for such detection (as is assumed in the cost-efficacy studies of screening, as previously discussed), and any such benefit is likely to be greatest in the high-risk groups, where the PPV of a positive screening test will be greatest. On this basis, therefore, it is generally assumed that the screening of high-risk groups is reasonable, but direct evidence for this is lacking at present, in almost all cases.

Special circumstances: High-risk groups

First-degree relatives. The prevalence of CD in first-degree relatives is around 10%,[16,137,138] with significantly higher prevalence figures in monozygotic twins, families with multiple persons affected, or siblings whom share the HLA susceptibility alleles.[139]

Type 1 diabetes. Up to one in three DQ2+ individuals with Type 1 diabetes expresses TTG.[140] Type 1 diabetes is also one of the most common autoimmune diseases in patients with CD,[92] and the relative risk for future Type 1 diabetes in patients with CD is estimated at 2.4.[141] Of note, that relative risk is almost identical to the future risk of Type 1 diabetes in whites whom are DQ2+,[142] suggesting that the increased risk of Type 1 diabetes may not be affected by dietary adherence. Between 2% and 12% of all Type 1 diabetes patients have CD.[16,99,143,144]

Iron-deficiency anaemia. CD may cause iron-deficiency anaemia through malabsorption, but also through an ongoing inflammation and potentially also through occult bleeding.[145,146] CD is also more common in patients with iron-deficiency anaemia and gastrointestinal symptoms including IBS,[147] and we suggest that both these risk groups undergo testing.

Down syndrome and Turner syndrome. Although most studies so far have been small, the prevalence of CD seems to be increased in both Down syndrome[148–150] and Turner syndrome.[151,152] The only direct analysis of screening cost-effectiveness in either of these conditions (of which we are aware) is by Swigonski et al.[153] This study, though it focuses on the prevention of lymphoma, does also address the total number of QALYs resulting from a screening strategy in this group. It is notable in suggesting that screening causes a reduction in QALYs, and though this is based on the assumption that having to eat a GFD represents a 1% reduction in QOL, that assumption is perhaps no more unreasonable than any considered in the analyses of general population screening, above.

Iron-deficiency anemia. CD may cause iron-deficiency anemia through malabsorption, but also through an ongoing inflammation and potentially, also through occult bleeding.[145,146] In addition, CD is more common in patients with iron-deficiency anaemia and gastrointestinal symptoms, including IBS;[147] and so we suggest that both these risk groups undergo testing.

Bone mineralization disorders, osteoporosis and osteomalacia. CD is associated with an increased risk

of fractures,[154–156] with relative risks of around 2 for fractures after CD diagnosis. An earlier study found a similar relationship (odds ratio around 2) for fractures prior to diagnosis, in patients with CD.[156]

Discussion and recommendations

There is an ethical difference between aggressive case-finding among the symptomatic, and screening for disease in the general population, where a diagnosis of CD in asymptomatic individuals may not confer clear benefits. Therefore, decisions on screening should be carefully considered. In this paper, we have tried to review the pros and cons of mass screening for CD against the established WHO criteria for mass screening, and a summary of key points in relation to screening is given in Table 4. Though CD meets many of these criteria, the outcome of undetected asymptomatic disease, the effect upon life expectancy and QOL with GFD in these patients; and therefore, the cost efficacy of screening, remains unclear. Screening-detected CD will have economic implications leading to both higher and lower costs, for the different actors; and whether mass-screening is economically sound is dependent on a number of assumptions. Though studies to date assuming that GFD improves quantity and QOL in the asymptomatic and is itself cost free, suggest that screening may be cost effective; to achieve certainty we would need more data, to reduce the number of such assumptions which must be made.

Neither the current National institute for Health and Care Excellence (NICE) guidelines[157] on the recognition and assessment of CD, nor the corresponding BSG guidelines,[14] recommend mass screening for CD in the UK; however, both guidelines do recommend that serological testing for CD should be conducted in a wide range of clinical situations, ranging from the presence of potential symptoms of the disease (diarrhea, failure of children to thrive, gastrointestinal symptoms, prolonged fatigue, sudden or unexpected weight loss, and anemia), through the presence of associated conditions (autoimmune thyroid disease, dermatitis herpetiformis, IBS, or Type 1 diabetes) or to the presence of CD in a first-degree relative.

Based on our literature review, we suggest that screening of high-risk groups may well be cost effective even if the benefit gained is small; however, proof of such benefit is still lacking. We recommend that future research should provide data on the outcomes of both undiagnosed and of treated asymptomatic CD.

In conclusion, we cannot recommend mass screening at the present stage. Though current diagnostic recommendations will only lead to the discovery of a minority of patients with CD, it is not yet clear that the detection of more of these cases would be of benefit to those detected.

Table 4. Key points: Screening for CD

CD occurs in about 1–2% of the Western population.
Varied presentations make CD difficult to diagnose, but there are screening tools available.
There are still few data on the complications that can occur from undiagnosed CD.
We recommend active case-finding, but not mass screening.

CD: celiac disease.

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Conflict of interest

TC had grant support from Coeliac UK, Crohn's and Colitis UK, and spouse is an employee of AstraZeneca. DSS has received an educational grant from Dr Schär (a gluten-free food manufacturer), to undertake an investigator-led research study on gluten sensitivity; and has also received an educational grant from both Biocard and Simtomax, to undertake an investigator-led research study on point-of-care tests.

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Appendix

PubMed search Jan 1, 1900 until June 1, 2014. Number of hits searching for "(Coeliac or coeliac)" and the below terms.

E.g. PubMed search:

**Abstracts and/or titles not examined in detail.*

Example of search strategy: ((coeliac or coeliac) and undiagnosed and (complications or comorbidity)) AND ("1900/01/01"[Date - Entrez]: "2014/06/01" [Date - Entrez])

Additional term	*Hits*
+Prevalence*	3612
+Definition	101
+Cultural	353
+Treatment *or* gluten*	141912
+Sensitivity and specificity*	1376
+Diagnostic delay	157
+Undiagnosed and (complications or comorbidity)#	123