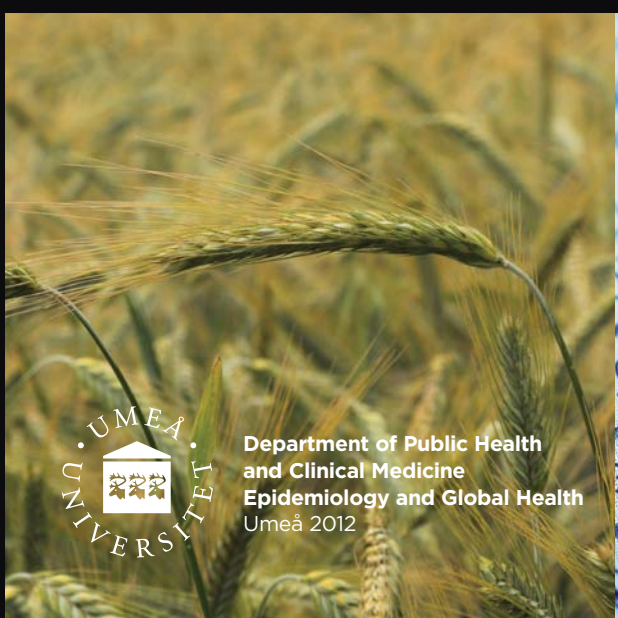
THE BURDEN OF **CELIAC DISEASE** AND THE VALUE OF HAVING IT DIAGNOSED

Fredrik Norström



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Abstract

Background: Celiac disease is a chronic disease characterized by intolerance to gluten. It is considered a public health problem affecting about 1% of Western populations, but, with most cases still undiagnosed. A gluten-free diet is the only effective treatment for the disease.

Objectives: To investigate the burden of celiac disease and the value of having it diagnosed. Additionally, the implications for a potential future celiac disease mass screening are discussed.

Methods: A questionnaire was sent during 2009 to 1,560 randomly selected adult members of the Swedish Society for Coeliacs, in equal-sized age- and sex strata, and 1,031 (66%) responded. Members were asked about symptoms, health-related quality of life as measured by EQ-5D, and health care consumption during the year prior to diagnosis and during the past year. They were also asked about the delay in having their celiac disease diagnosed and the appearance of other immune-mediated diseases.

A school-based celiac disease screening of 12-year-olds was performed during 2005-2006. After blood sampling the 7,567 participating children and their parents received a questionnaire including the EQ-5D instrument in order to measure the child's health-related quality of life. Comparisons were made between children with screening-detected celiac disease, those with previously diagnosed disease and those without the disease. Parents were asked about their willingness to pay for a celiac disease screening of their child, which was compared with the actual cost of a screening.

Results: Adult celiac disease patients had a poorer health-related quality of life than the general population, and a high prevalence of symptoms before celiac disease diagnosis. The mean delay from symptoms to diagnosis was 9.7 years. After initiated treatment with a gluten-free diet, health-related quality of life was improved to the level of the general population, and symptom relief and reduction in health care consumption were also reported. For children, health-related quality of life was similar across groups. The average cost per child for a screening was 47 EUR. Parents' mean willingness to pay for a screening was 79 EUR, median 10 EUR.

Conclusion: The delay in celiac disease diagnosis is long, and treatment with a gluten-free diet substantially improved health for clinically detected cases. For screening-detected celiac disease the health benefits are still uncertain. A mass screening might nevertheless be justified to avoid the burden of living with undiagnosed disease, and parents' willingness to pay indicates that performing it in childhood might be economically motivated. However, as both the cost-effectiveness of a screening and the short- and long term health benefits for screening-detected cases have not yet been sufficiently investigated, it is too early to make a recommendation for a celiac disease mass screening.

Abbreviations

atTG - Anti-human tissue transglutaminase
DALY – Disability-adjusted life year
ESPGHAN – European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
EMA – Endomysial antibodies
ETICS – Exploring the iceberg of celiacs in Sweden
EQ-5D – EuroQol five dimensions
EQ-5D-Y – EuroQol five dimensions youth
HRQoL – Health-related quality of life
SF-12 – Short Form 12
SF-36 – Short Form 36
WHO - World Health Organization
WTP – Willingness to pay
QALY – Quality adjusted life year

Populärvetenskaplig sammanfattning

Celiaki, även kallat glutenintolerans, är en kronisk sjukdom som kännetecknas av att tunntarmens slemhinna skadas av gluten som finns i vete, råg och korn. Den enda effektiva behandlingen av sjukdomen är en glutenfri kost. Förekomsten av celiaki har under de senaste årtiondena räknats upp flera gånger. Idag är den allmänna uppfattningen att ungefär 1% av befolkningen i västvärlden har sjukdomen. Fortfarande har merparten av dessa inte fått en medicinsk diagnos. Tidigare var celiaki en okänd sjukdom för de flesta svenskar, men är nu känd bland många. Celiaki anses idag som ett folkhälsoproblem i stora delar av världen.

Celiaki har kopplats till diverse hälsoproblem. En del sjukdomar är vanligare bland personer med celiaki som t.ex. diabetes typ I och sköldkörtelsjukdomar. Traditionellt förknippas celiaki med magrelaterade symptom och då framför allt diarré. Numera är det känt att de flesta har s.k. atypiska symptom som blodbrist och trötthet och många saknar helt magbekymmer. Det varierande uttrycket av sjukdomen och att en del helt tycks sakna besvär bidrar till att det ofta tar många år innan man får sin diagnos. En möjlighet för tidigare diagnos är att med blodprov genomföra en massundersökning av befolkningen. Det skulle rentav kunna vara enda möjligheten för vissa att få en diagnos under sin livstid.

I min avhandling är huvudsyftet att undersöka bördan av att leva med celiaki och värdet av en celiakidiagnos. Utöver detta diskuteras även en möjlig framtida massundersökning för celiaki. Avhandlingen omfattar två studier: i) en enkätstudie till vuxna med celiaki och ii) en skolbaserad screening för celiaki av barn i årskurs 6. I vuxenstudien skickades en enkät ut till 1560 medlemmar i svenska celiakiförbundet och den besvarades av 1031 (66%) personer. Enkäten innehöll frågor om hälsorelaterad livskvalitet, symptom och sjukvårdskonsumtion. I barnstudien inbjöds 10041 barn och 7567 barn deltog efter sina föräldrars godkännande. Merparten av både deltagande barn (95%) och deras föräldrar (86%) svarade på varsin enkät. I båda enkäterna besvarades frågor om barnets hälsorelaterade livskvalitet. Föräldrarna fick också ange hur mycket de skulle vara villiga att betala för en celiakiundersökning av sitt barn.

I vuxenstudien fann vi att obehandlad celiaki medför dålig hälsa, både uttryckt i symptom och hälsorelaterad livskvalitet. Det tog i genomsnitt 10 år från första celiakirelaterade symptomet till en diagnos och trots en förbättring över tid så tar det ännu idag lång tid innan många får sin diagnos. Det har visats i andra länder att läkare har dålig kännedom om celiaki och det är troligt att en bättre kännedom om sjukdomen hos svenska läkare skulle minska tiden till diagnos. Omfattningen av symptom minskade och den hälsorelaterade livskvaliteten förbättrades till samma nivå som för övriga befolkningen efter diagnos och påbörjad behandling. En diagnos

innebar också minskad sjukvårdskonsumtion vilket talar för en besparing för både individen och samhället.

I barnstudien var den hälsorelaterade livskvaliteten likvärdig för barn med behandlad celiaki och barn utan celiaki vilket stärker bilden av att en diagnos innebär förbättrad hälsa. Också de barn som diagnostiserades via vår screening uppvisade en hälsorelaterad livskvalitet som var likvärdig med den för barn utan celiaki. Det behöver inte betyda att grupperna har likvärdig hälsa. Istället kan metoden för att mäta hälsorelaterad livskvalitet vara för oprecis för att upptäcka skillnader, eller också kan barnen ha överskattat sin hälsa för att de vant sig vid att må sämre. Liknande resultat har också visats för vuxna med celiaki upptäckt via screening. Det behövs fler studier för att utvärdera hälsovinsten från en diagnos via massundersökning.

Föräldrarna fastställde sin betalningsvilja för en screening av celiaki utifrån en beskrivning av sjukdomen. Den faktiska kostnaden för en massundersökning beräknades till 470 kronor per barn, vilket är mindre än föräldrarnas betalningsvilja som i genomsnitt var 790 kronor. Det är värt att nämna att endast 23% av föräldrarna var villiga att betala den faktiska kostnaden.

En massundersökning kräver att vissa villkor är uppfyllda. Bland annat är det viktigt att känna till hur sjukdomen utvecklas (naturalförloppet) och om undersökningen är kostnadseffektiv. Avhandlingen visar att de som får celiakidiagnos via klinik förbättrar sin hälsa efter påbörjad behandling. Däremot behöver de kort- och långsiktiga hälsovinsterna för de som diagnostiserats via en massundersökning undersökas ytterligare. För både kliniska och screening-upptäckta fall är det fortfarande oklart om de relaterade autoimmuna sjukdomarna kan förebyggas genom behandling. Det är också oklart om en massundersökning av celiaki är kostnadseffektiv. Denna avhandling bidrar med värdefull kunskap för en mer fullständig hälsoekonomisk utvärdering av celiaki än tidigare gjorts genom att undersöka betalningsviljan, kostnaderna för en massundersökning och de eventuella sjukvårdsbesparingarna från en diagnos. Innan ett ställningstagande till en eventuell framtida massundersökning för celiaki kan göras vore det även värdefullt med fler studier som undersöker acceptansen för både screeningen och den glutenfria kosten.

Original papers

This thesis is based on the following papers:

I. **Norström F**, Sandström O, Lindholm L, Ivarsson A. A gluten-free diet effectively reduces symptoms and health care consumption in a Swedish celiac disease population. (*Submitted).*

II. **Norström F**, Lindholm L, Sandström O, Nordyke K, Ivarsson A. Delay to celiac disease diagnosis and its implications for health-related quality of life. *BMC Gastroenterology* 2011;11:118.

III. Nordyke K, **Norström F**, Lindholm L, Carlsson A, Danielsson L, Emmelin M, Högberg L, Karlsson E, Ivarsson A. Health-related quality-of-life in children with coeliac disease, measured prior to receiving their diagnosis through screening. *Journal of Medical Screening* 2011;18:187-192.

IV. **Norström F**, Ivarsson A, Lindholm L, Carlsson A, Danielsson L, Högberg L, Karlsson E, Löfgren C. Parents' willingness to pay for coeliac disease screening of their child. *Journal of Pediatric Gastroenterology and Nutrition* 2011;52:452-459.

Background

About celiac disease

Gluten intolerance

Celiac disease, also called gluten intolerance, is a chronic disease. The cause of the disease was long unknown, although it was believed at an early stage that diet played a role [1]. It was not until 1950 that Dicke showed evidence that wheat triggered the disease [2,3]. The link to gluten, and more specifically wheat gluten and related proteins in rye and barley, was later proven.

Exposure to dietary gluten induces an immune reaction that results in inflammation and atrophy of the small intestinal mucosa. A life-long strict gluten-free diet is the only available effective treatment for the disease [4]. After initiated treatment the small intestinal mucosa usually recovers [4], but there are also cases of nonresponsive celiac disease [5]. For adult patients it is rare that the small intestinal mucosa completely recovers with a gluten-free diet [6,7]. It is not possible to keep all food products 100% gluten-free. It is believed that less than 10 mg of gluten on a daily basis is tolerable for celiac disease patients [8].

Clinical manifestations

Samuel Gee, published an early description of celiac disease in 1888, characterizing the disease as diarrhea in young children [1]. Interestingly, he also noted that it sometimes appeared among sailors, but seldom among other adults. The strong association with diarrhea lasted for a long time. As recently as 30 years ago malabsorption was the predominant reason for a celiac disease investigation [4]. In the 1980s, over 70% of those with celiac disease in New York were reported to have diarrhea as the initial presentation [9]. Among other typical, or so-called classical symptoms were abdominal pain and failure to thrive. Over time the spectrum of symptoms associated with celiac disease has widened and the proportion with classical symptoms has decreased [4,9-14]. Nowadays, signs and symptoms usually called atypical are common in the disease presentation, e.g. constipation, anemia, fatigue, depression, infertility and osteoporosis.

Diagnostics

It was not until the 1950s that histological changes in the duodenal mucosa of celiac disease patients were demonstrated in small intestinal biopsies [15]. In Sweden, the small intestinal biopsy was introduced in routine clinical work in 1967 [16]. Today, the gold standard for setting a celiac disease diagnosis is the small intestinal biopsy with grading of the condition of the mucosa. The Marsh-Oberhuber classification is commonly used [17].

Recommendations from ESPGHAN have commonly been followed, with villous atrophy and clinical improvement on a gluten-free diet required for

diagnosis [18]. During recent years, minor enteropathy combined with clinical signs have also been used for diagnosis [19]. The level of mucosal damage, which can also be patchy [20], makes a diagnosis difficult in some cases. To improve accuracy, Green and Cellier recommend taking at least 4-6 biopsy specimens [21]. In most recent pediatric recommendations, biopsies from both the duodenal bulb and the descending duodenum are recommended [22].

In early celiac disease studies serology tests were not available or in use in clinical work [16,23-26]. During the late 1960s and early 1970s the search for useful serological markers as a diagnostic tool for celiac disease was intensified, and several markers were suggested [27]. Over time has markers been developed and improved. Nowadays, antigliadin antibodies, anti-endomysium antibodies, and anti-transglutaminase antibodies are the most commonly used serological markers for celiac disease in commercial laboratories [28]. Serology has become an important component in investigating the disease, and based on these markers a small intestinal biopsy can be recommended. The latest guidelines from ESPGHAN emphasize that a celiac disease diagnosis is based on a combination of history, serology, and histopathology [22].

Long delay in diagnosis of celiac disease

A long delay from the first celiac disease-related symptoms to a diagnosis has been reported in several countries. Studies in the United States, the United Kingdom (UK) and Canada have reported the average delay from symptoms to diagnosis to be 11-13 years [29-31]. Other studies have reported a delay of 5-6 years in Italy, in Germany, and in the United States, respectively [9,32-34]. A decreased delay in diagnosis has been reported over time [9,30], but also no signs of a decrease over time [29]. In recent decades increased knowledge has been attained about a wider range of celiac disease-related symptoms in both children and adults, and along with improved facilities for diagnostics, this has resulted in a higher mean and median age at the time of diagnosis [9,11,12].

Heredity and environmental factors

Virtually all celiac disease patients share the same genetic predisposition, as they either express the HLA-DQ2 or HLA-DQ8 molecule. These molecules are believed to be a necessity for developing the disease, however, only a minority of carriers develop celiac disease [35]. Thus, also other genetic and environmental risk factors are involved in the development [36]. Infant feeding practices are an environmental factor shown to influence the risk of having celiac disease early in life [37-39]. Nevertheless, few environmental factors that influence the risk of having celiac disease have been identified [36].

How common is celiac disease?

Prevalence of celiac disease

Despite the fact that celiac disease was described in sailors by Gee [1], it was considered a childhood disease until just a few decades ago. Celiac disease was also described as a rare disease, with an early study reporting a prevalence in the late 1940s of 0.125 per 1,000 persons in England & Wales and 0.25 per 1,000 persons in Scotland [23,24]. In the first Swedish prevalence study performed in 1964 a similar low prevalence of 0.16 cases per 1,000 children was reported [40]. In 1972, after introduction of the small intestinal biopsy, the prevalence of celiac disease was reported to be 1.7 cases per 1,000 children in West Ireland [24]. In Sweden, the first studies with biopsy-proven cases reported a prevalence ranging from 1 to 1.4 cases per 1,000 children [16,25,26]. It was believed that a more active diagnostic approach and the introduction of the small intestinal biopsy might explain this increase [16,24].

Over time it became apparent that celiac disease also affects adults [9]. The first Swedish study in adults (age above 15 years) reported a prevalence of 0.27 biopsy-proven cases per 1,000 in 1979 [41]. In a different catchment area, a prevalence of 1.0 biopsy-proven cases per 1,000 adults was reported in 1986 [42]. The first celiac disease screening of the general population using serological tests, was performed in healthy blood donors in the 1980s, and it revealed a prevalence of 3.9 cases per 1,000 [43]. However, the screening-detected cases were not verified by a biopsy. Clinically detected celiac disease in that study was 1.0 biopsy-proven case per 1,000 adults, which was similar to the previously cited Swedish study [42]. In 1994, the first and only population-based screening of Swedish adults revealed a prevalence of 5.3 biopsy-proven cases per 1,000 adults [44].

Nowadays, celiac disease is not considered a rare disease. A review of celiac disease studies showed a biopsy-proven prevalence ranging from 0.15% to 1.9% in unselected populations of North America and Western Europe [45]. It was concluded that the prevalence of celiac disease in the general population is about 1%, and somewhat higher in some populations. The highest reported biopsy-proven prevalence is 3%, which was revealed among Swedish children [46], and based on serology alone it is 5.6%, which was revealed among children in a refugee camp in Algeria with high exposure to wheat [47]. It is generally agreed that the prevalence of celiac disease in the latter population is the highest thus far in an unselected population.

Screening studies have revealed a large proportion of undiagnosed cases of celiac disease. Fasano and Catassi reported 5-10 undiagnosed celiac disease cases for each diagnosed case in Western countries [48]. In Sweden, it has been reported that 4 out of 5 adults with celiac disease [44], and 2 out of 3 children with the disease [46], are undiagnosed.

The Swedish epidemic

There was a national recommendation at the end of 1982 to postpone the introduction of gluten to infants from 4 until 6 months of age [49], and at the same time the gluten content in baby food products was increased [49,50]. Following these changes, a unique increase in the incidence of celiac disease in children below 2 years of age was reported [51-53]. At that time, celiac disease was generally believed to be unavoidable in genetically predisposed individuals [54-56] , and therefore the increase in incidence was unexpected. There was discussion concerning whether it would be appropriate to actually provoke the disease so as to diagnose it earlier in life [54-57].

Due to the increase, the Swedish childhood coeliac disease working group, with one pediatric gastroenterologist from each of seven health care regions in Sweden, was formed [50,58]. The first mission was to collect data about the incidence of childhood celiac disease in Sweden. A national Swedish childhood celiac disease register was started, covering 14 pediatric clinics, and their work confirmed the increase in childhood celiac disease [58]. Based on the national incidence register, a rise in the annual incidence between 1985 and 1987 was detected in those below 2 years of age, and this remained at a high level until finally returning to the previous level in 1997. This period with an increase followed by a decrease in incidence is called the Swedish epidemic of celiac disease [49]. The start of the Swedish epidemic has partly been explained by the more frequent introduction of gluten after breast-feeding had ended (and not age as such), and an increase in gluten in baby foods [37].

The national recommendation for gluten introduction was changed again in 1996, and a gradual introduction of gluten, preferably while breastfeeding was still ongoing, was recommended, and at the same time the amount of gluten in baby food was decreased. Following these changes the incidence of celiac disease in children under two years of age returned to the previous low level [49]. The incidence is still on a much lower level than during the epidemic years, but there are signs of an increasing trend in children below two years of age [59].

The cumulative incidence of celiac disease also remains higher for children born during the epidemic years when they get older as compared to other birth cohorts [59]. However, it is not known whether the true celiac disease prevalence also differs, i.e. the prevalence of diagnosed and unrecognized cases, with the latter referring to children who have the disease without being aware of it. To investigate if there is a difference in prevalence between children born during the epidemic years and the years thereafter, a two-phase school-based screening study of 12-year-old children was initiated. The first phase was performed during 2005-2006 and revealed a celiac disease prevalence of 3% [46]. The second phase was performed during 2009-2010, with the prevalence yet to be published.

Morbidity and mortality in celiac disease

Celiac disease is considered an immune-mediated disease, and a relation to other immune-mediated disease has long been known [60,61]. Anemia, bone-related problems and deficiencies related to malnutrition are common in untreated celiac disease. Recently, neurological and psychiatric disorders and their potential relation to celiac disease have received a good deal of attention [4].

Most studies have shown a more frequent occurrence of autoimmune thyroid disorders in celiac disease patients than in the general population [62-65], and the same has also been shown for celiac disease among thyroid patients [66-71]. It has been found that the prevalence of celiac disease is higher among thyroid patients with other immune-mediated diseases than in patients without such diseases, and it has been suggested that there might be an indirect rather than a direct link through other disorders between celiac disease and autoimmune thyroid disease [66,70].

The association with diabetes mellitus type 1 was noted as early as 1951 [72]. Later studies have confirmed that celiac disease is more frequent among diabetes mellitus type 1 patients than in the general population [45,73,74]. Sharing HLA-DQ2 as genetic factor is one explanation for the higher prevalence of celiac disease among diabetes mellitus type 1 patients [75].

Screening studies have shown a higher prevalence of inflammatory bowel disease in celiac disease patients than in the general population [76-79]. However, studies have also shown a similar or lower prevalence of celiac disease in inflammatory bowel disease patients compared to controls [79,80], with contradictory results from one study [81]. Celiac disease and inflammatory bowel disease have genetic similarities, which might explain the potential relation between the diseases [82].

A relation has been shown to primary biliary cirrhosis [83,84], and celiac disease is common in both adults and children with hypertransaminasemia and other liver disorders [85].

An association between celiac disease and arthritis has been reported [86,87], but not confirmed [88-91]. As is the case with celiac disease and inflammatory bowel disease, common genes have been detected in patients with celiac disease and/or rheumatic arthritis, but their role in the development of both diseases has to be further investigated [92].

Dermatitis herpetiformis, which is characterized by an itching and blistering skin, is a common manifestation of celiac disease. The highest reported prevalence of dermatitis herpetiformis is 75.3 cases per 100,000 population [93], or 12% of celiac disease patients [93,94]. There are indications that celiac disease coexists with the skin diseases alopecia areata [95], vitiligo [96,97], aphthous stomatitis [98], and psoriasis [99,100]. However, there is only good evidence for the association with psoriasis [100].

A high prevalence of celiac disease has been reported in multiple sclerosis patients and their relatives [101]. In a register-based study, Ludvigsson and

colleagues investigated neurological diseases in celiac disease. The only positive relation seen was with polyneuropathy; interestingly, no association was detected with multiple sclerosis, Parkinson's disease, Alzheimer's disease, hereditary ataxia, symptom ataxia, Huntington's disease, myasthenia gravis or spinal muscular atrophy [102]. Other neurological diseases with strong evidence of a co-existence with celiac disease are cerebellar ataxia (also called gluten ataxia), peripheral neuropathy, epilepsy and migraine [103,104].

There is a well established connection between celiac disease and bone disorders [105]. Bone mineral density is lower for celiac disease patients than for the general population [106,107], and the risk of osteoporosis [108-111] and fractures is increased [112-115].

Celiac disease seems to be related to psychiatric disorders, but there is a need for further investigation within this field. Most studies have reported a higher prevalence of depression in celiac disease patients, while the risk, if any, for anxiety in celiac disease patients is likely to be low [116,117]. Studies indicate an increased risk of developing schizophrenia among celiac disease patients [118,119]. The only study on the relationship with bipolar disorder found no evidence for a connection with celiac disease [120].

Celiac disease and irritable bowel syndrome, a functional gastrointestinal disorder, display symptoms impossible to distinguish from each other. Serological markers indicative of celiac disease are included in the investigation of irritable bowel syndrome. In a meta-analysis by Ford and colleagues a four times higher prevalence of celiac disease was reported for irritable bowel syndrome patients as compared to the general population [121].

Celiac disease is associated with an increased risk of some malignancies. Tio and colleagues reported in a meta-analysis an increased risk of having non-Hodgkin lymphoma (risk estimate 2.6), T-cell non-Hodgkin lymphoma (risk estimate 16), lymphoproliferative malignancy (risk estimate 2.5), Hodgkin lymphoma (risk estimate 2.0) and diffuse large cell lymphoma (risk estimate 2.2), but not chronic lymphatic leukemia or diffuse large cell lymphoma [122]. Interestingly, their risk estimate for any malignancy was not significantly higher for celiac disease patients than for the general population. An increased risk has been reported for papillary thyroid cancer [123,124], while breast cancer seems to be less frequent in celiac disease patients [125,126].

Tio and colleagues also reported an increased mortality risk estimate of 1.24 in celiac disease patients [122]. The mortality risk for unrecognized celiac disease has been based on serology, and these studies have found both an increased mortality risk [127-129] and no difference in mortality risk [130-132]. Mortality in celiac disease has not been studied in Africa or Asia. A recent study estimated that unrecognized celiac disease might be responsible for about 4% of the global childhood diarrheal mortality [133].

Effect of gluten withdrawal

In addition to the effective treatment of celiac disease, a gluten-free diet has been suggested to have many other positive health effects, even in people without celiac disease, e.g. for those with functional gastrointestinal disorders [134]. Regarding some potential future complications, this makes it more difficult to study whether gluten withdrawal is preventive due to celiac disease being treated or if it is due to other reasons.

Ventura and colleagues reported that the prevalence of immune-mediated diseases increases with age at celiac disease diagnosis. They therefore proposed that longer exposure to gluten increases the risk of developing immune-mediated diseases [61]. Their proposal has not been verified [135], and contradictory results exist, i.e. a preventive effect from gluten exposure [136]. The role of gluten is still unclear in related immune-mediated diseases [61,135-137].

Studies have also focused on specific immune-mediated diseases. Gluten removal seems to normalize antithyroid antibodies [64,138], but does not decrease the risk of thyroid disease [63,138]. Ventura and colleagues showed that a gluten-free diet might prevent the appearance of diabetes mellitus type 1 [61], but this has not been confirmed [74,135]. The role of the gluten-free diet in glycemic control in diabetes mellitus type 1 patients has been shown to be both favourable [139], and unfavourable [140,141].

A gluten-free diet has a positive effect on dermatitis herpetiformis patients [93]. A positive effect has also been shown in psoriasis patients [142,143]. Case reports have indicated an improvement in alopecia areata [144], and vitiligo with the diet [145]. For liver diseases the value of a gluten-free diet is unclear [85,146].

A gluten-free diet can normalize bone mineral density, but a diagnosis at a young age seems necessary for complete recovery [147]. There is a lack of evidence for a reduced risk of fractures [113-115].

The protective role of a gluten-free diet for the risk of depression and anxiety is unclear [117,148,149]. Schizophrenic patients have experienced a positive effect from a gluten-free diet, but this might be independent of celiac disease, i.e. the gluten-free diet may have another role in the development of schizophrenia, but such an association has been questioned and further investigations are needed [119].

It has long been believed that a gluten-free diet prevents the development of malignancies [32,150,151]. However, conclusions have been based on few cases, and the study with the most cases (n=59) of malignancy resulted in doubt about a preventive effect [152].

Screening

Background

As early as 1861, Dr Horace Dobell suggested that everyone undergo periodic checks of their health. In a scientific paper published in 1900 Gould proposed annual examinations, primarily for the purpose of enhancing knowledge about diseases and their prevention. Many routine examinations and screening programs were implemented in the first half of the 20th century, but it was not until the 1960s that they focused more on the value of health. Even in the 1990s the health benefits of a screening program were not always clear. Nowadays it is considered important for a screening program to be evaluated before being implemented [153].

There is no general definition of a medical screening. Nicholas Wald, editor of the Journal of Medical Screening, proposed the following definition: "Screening is the systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder." [154].

Suggested principles

In 1968, on behalf of the World Health Organization (WHO), Wilson & Jungner suggested 10 principles for case finding as listed below [155].

1) The condition should be an important health problem
2) An accepted treatment of the disease for patients should be recognized
3) Facilities for diagnosis and treatment should be available
4) There should be a recognizable latent or early symptomatic stage
5) There should be a suitable test for disease detection
6) The test should be acceptable for the public
7) The natural history of the condition, including the development from latent to declared disease, should be adequately understood
8) There should be an agreed policy on who to treat as patients
9) The cost of case-finding should be economically balanced in relation to possible expenditure as a whole
10) Case-finding should be a continuous process

Their principles are still frequently referred to within the field. They do not explicitly mention that case finding should be cost-effective [155], but this is the underlying message from the reasoning of the ninth principle. The principles Wilson and Jungner suggested should also be in accord with the definition of medical screening by Wald [154], as well as for a celiac disease mass screening, even if they do not explicitly mention screening.

Should everyone be screened for celiac disease?

A celiac disease mass screening has long been debated [156]. There are arguments by Fasano favouring a screening [157,158], and arguments against it by other researchers [159-162]. Fasano motivated his view based on a more comprehensive recommendation from WHO, and did not consider Wilson and Jungner's cost-effectiveness principle [155]. It is generally agreed that most of the principles are fulfilled for a celiac disease mass screening [159,163].

The principles most at issue are the natural history of the disease for those detected by screening, and the cost-effectiveness of a mass screening. Most long-term health benefits have been studied for clinically-detected cases, while there is a large knowledge gap for screening-detected cases, both regarding their future health if not detected by a screening and their long-term health benefits if detected by a screening. Screening-detected cases also face the challenge of complying with a strict gluten-free diet, which might even decrease their quality of life [164]. Another important aspect of a mass screening is the age that is suitable for a screening, and whether performing it once in a lifetime is sufficient [165].

Celiac disease and health economics

Economic evaluation

In 1996, Richard Logan wrote that the relation between costs and benefits of a celiac disease mass screening must be assessed before a decision can be made about implementation [156]. However, he thought that its acceptability and effectiveness should be assessed first. Drummond and co-authors recommend that in order for an economic evaluation to be reasonable, the efficacy, effectiveness and availability of an intervention should first be evaluated, which is in accord with Logan's statement [166].

Drummond and co-authors define economic evaluation as "the comparative analysis of alternative courses of action in terms of both their cost and consequences" [166, p.9]. This implies that any intervention, e.g. a celiac disease mass screening, should only be implemented if the intervention is cost-effective, i.e. costs are acceptable in relation to the health gain. In economic evaluations, an intervention can be compared with another intervention with the same objective, but also with an intervention in a different area, such as comparing a celiac disease mass screening with an intervention in elderly care [166]. To compare interventions in different areas, a generic health measure is needed.

Drummond and co-authors divide economic evaluations into four groups: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis [166]. In a cost-minimization analysis the outcomes of the interventions under study are identical and the preferred intervention is the one with the lowest cost. The cost-effectiveness analysis measures effects in natural units and resources in monetary units. Interventions are compared based on the cost per effect unit, e.g. the cost per life year saved. In a cost-utility analysis, the utility is commonly measured by quality-adjusted life year (QALY) scores, with scores ranging from 0 (death) to 1 (full health). Interventions are then compared by cost per gained utility unit, e.g. cost per gained QALY. In Figure 1, the potential QALY scores after a celiac disease mass screening are illustrated as well as the scores associated with the natural history if not screened. In a cost-utility analysis, gained QALYs for those detected by a mass screening are divided by the cost for a mass screening.

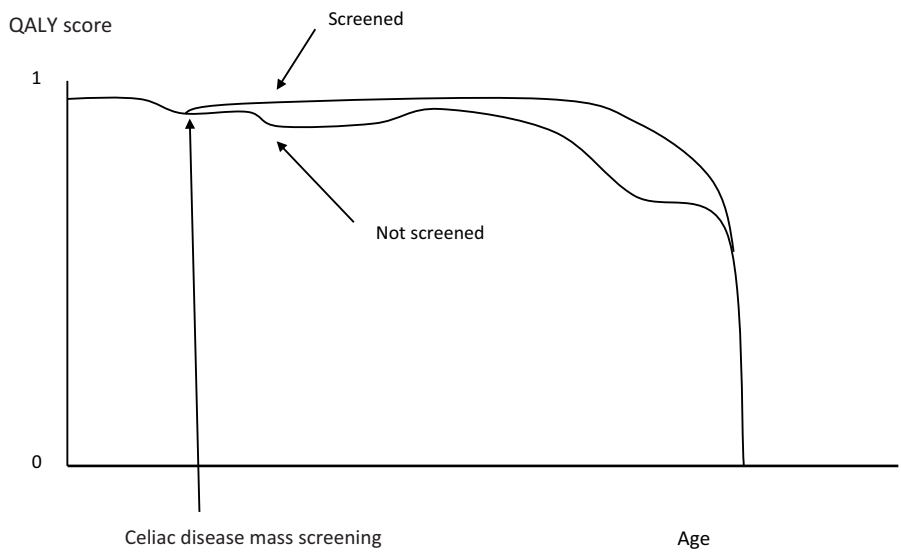

Figure 1. Potential health-related quality of life scores, as expressed in quality-adjusted life year (QALY) scores, for the lifetime of a person with celiac disease. The upper line is a hypothetical prediction if diagnosed by screening and the lower line is a prediction if not screened.

For both cost-effectiveness and cost-utility analyses, a budget constraint is assumed and the basic idea is to use the existing budget in an optimal way, i.e. to maximize the health of the population [166]. A cost-benefit analysis differs from the methods described above in that it measures the absolute benefit of an intervention in monetary terms, while the other interventions measure benefits in relation to health effects [166].

Measuring intervention costs

In measuring the cost for an intervention, in principle all related costs should be considered. Therefore, when calculating the total cost of the intervention, not only the most direct and obvious costs of the intervention itself should be included. A celiac disease mass screening should not only consider the cost for analyzing the blood samples and performing small intestinal biopsies, but also, for example, working hours for personnel and increased costs for the food (a gluten-free diet is usually more expensive [167]). Difficulties in obtaining proper cost estimates can be a reason for excluding them, but when any cost item is excluded it must be likely that it has little influence on the outcome of the evaluation.

Drummond and co-workers separate costs for resources consumed for an intervention into four broad areas: i) health sector, ii) other sectors, iii) patient and family, and iv) productivity losses [166]. For a celiac disease mass screening the broad areas could be exemplified with: i) the health sector being responsible for the diagnoses, ii) the municipalities employ school nurses, iii) families have to pay for the gluten-free diet, and iv) untreated celiac disease can influence a person's working capacity. An economic evaluation can consist of all of the cost items within the four areas or be more limited and exclude, for example, costs to the patient and family. In economic evaluations a perspective is usually chosen such as societal or health care. In the societal perspective all sectors are included, while in a health care perspective only the costs for the health sector are included.

It is also important to consider costs that will be ongoing after implementation of the intervention, as they might influence the costs for the individual or health sector for years. For example, if given a celiac disease diagnosis in a mass screening, future complications might be avoided and thereby the cost for both individuals and health care might be lowered for succeeding years. Thus, a crucial factor in an economic evaluation is the future costs and savings from the intervention. The four previously mentioned broad areas of consumed resources are equally valid for future costs and savings of an intervention.

Measuring effects and values of an intervention

In an analysis, the effect is measured and there is an attempt to put a value on the intervention. A common way of measuring the effect of an intervention is to count life years saved or disability days reduced. Drummond and co-workers divide the value of an intervention into three categories: i) the change in health state can be valued by a health state preference measure such as QALYs and/or by the willingness to pay (WTP), ii) other values created such as information can be valued by the WTP for it, and iii) the value of resources saved [166].

The health state preference, e.g. health-related quality of life (HRQoL), can be measured by generic instruments. Perhaps the most popular instruments for measuring HRQoL today are the Short Form 36 (SF-36) and the EuroQol 5 dimensions (EQ-5D). The SF-36 instrument includes eight

multi-item measures, all representing different aspects of health, and it can be reduced to the Short Form 12 (SF-12) [168]. The EQ-5D instrument consists of a descriptive system, including five health-related dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a visual analogue scale (EQ VAS), which independently measures HRQoL [169]. Each of the five health-related dimensions has three levels of severity, corresponding to no problems, moderate problems and severe problems.

Both the SF-36 and the descriptive system of EQ-5D can be translated to a QALY score [166]. For EQ-5D, the first developed tariff for QALY scores, or the EQ-5D index as it is also called [169], was for the UK [170], and later tariffs were developed for other countries as well, including the United States [171]. A Swedish tariff has been developed [172], but it is based on a rather small population [173], and instead the UK tariff has commonly been used for the Swedish population [170].

Other values can be related to knowledge about health status provided from a screening. The value of resources saved relates to savings within the health sector, other sectors, patient and family, and the productivity gains from an intervention.

The willingness to pay approach

The WTP approach is commonly used in cost-benefit analysis [174,175]. In this approach, the responder is asked to state the amount he/she is willing to pay for a good, service or amenity, based on a well-defined scenario [174,175]. The formulation of the scenario is of great importance, because if it is poorly described the responder could be misled. Even with a well described scenario there is a risk of misunderstanding it that is associated with a hypothetical bias [176].

The format for how to respond to the WTP question is also of great importance. The probably most commonly used formats are the open-ended format, the closed-ended format and the payment scale approach [177]. The open-ended format only requires the statement of an amount, while the closed-ended format requires a yes or no to a specific amount, and the payment scale approach forces the responder to choose WTP among a list of alternative amounts. The WTP approach has previously been used within other areas of health care [178], but not for celiac disease.

Celiac disease and health-related quality of life

It was not until 1998 that the first study was published about health-related quality of life for celiac disease patients [179]. Since then interest in the field has increased. SF-36 (or the shortened SF-12) has been the most popular instrument [33,164,179-184], but recently EQ-5D has also been used in some studies [30,185]. Disease-specific HRQoL instruments for celiac disease have also been developed, both for adults [186,187] and for children [188,189], but until now they have been sparsely used.

Most studies on celiac disease have shown similar HRQoL as in the general population after initiated treatment with a gluten-free diet [30,181,183,184,188,190], although some studies indicate worse HRQoL despite initiated treatment [33,182]. Compliance with the gluten-free diet seems to have a positive effect on HRQoL [182,185,191], but there are also indications that difficulties in adhering to the diet are related to a worsened HRQoL [164].

In a study in the UK it was concluded that HRQoL was similar to that of stroke patients before treatment [30]. HRQoL has also been reported as worse at the time of diagnosis for asymptomatic celiac disease patients compared to controls [183,192]. The burden of celiac disease, as measured by HRQoL, has been shown to be greater for females than males both before [30], and after diagnosis [30,179,184,193]. Compliance with the gluten-free diet and being male are the factors most strongly associated with an improved HRQoL after celiac disease diagnosis, and the effects of few other factors are documented.

Economic evaluations within the celiac disease field

Few economic evaluations have been done for a celiac disease screening of the general population. Shamir and colleagues used a cost-effectiveness analysis and measured cost per life-year gained [194]. The same research team later refined their approach with a cost-utility analysis and presented results as cost per QALY gained [195]. In both studies a celiac disease mass screening was considered cost-effective, but this then required that all of the assumptions used in their model were correct [194,195]. Economic evaluations have also been done for celiac disease risk groups.

- Diabetes
  - Dretzke and colleagues suggested celiac disease screening for those with diabetes mellitus type 1 [196].
  - The National Institute for Health and Clinical Excellence used some evidence from the above study. Their conclusion was also to suggest a screening for celiac disease in the risk group [197].
- Irritable bowel syndrome
  - Spiegel and colleagues considered a screening to be cost-effective based on a celiac disease prevalence above 1% [198].
  - Mein and colleagues considered a screening to be cost-effective even with a relatively low celiac disease prevalence and a small gain in quality of life with a gluten-free diet [199].

There have also been economic evaluations based on comparing serological tests for clinical screening of symptomatic patients, without involving the mass screening perspective [200-202].

Costs related to celiac disease have rarely been investigated within the celiac disease field. It is known that diagnosed individuals are likely to face an increased cost for food after diagnosis [167,203], but also a decreased cost from reduced use of health care [204]. The reduced use of health care will mainly be a societal savings, but the individual will also benefit. Previous economic evaluations of a celiac disease mass screening, as well as screening of risk groups, have been limited mainly to costs for serological markers [194,195]. The complete economic consequences of a celiac disease diagnosis have never been studied, and in particular there is a lack of studies considering health care consumption before and after a celiac disease diagnosis [204,205].

Aims

The overall aim of the thesis is to investigate the burden of celiac disease and the value of having it diagnosed. Additionally, the implications for a potential future celiac disease mass screening are discussed.

Specific aims

- To investigate the effect of a gluten-free diet on celiac disease related symptoms, health care consumption, and the risk of developing associated immune-mediated disorders (Paper I).
- To determine how the delay in diagnosing celiac disease has developed during recent decades and how this affects the burden of disease in terms of health-related quality of life, and also to consider differences with respect to sex and age (Paper II).
- To compare the health-related quality of life of children with screening-detected celiac disease, before they learned of their diagnosis, with that of children without celiac disease and in those previously diagnosed with celiac disease (Paper III).
- To determine Swedish parents' willingness to pay for celiac disease screening of their child (Paper IV).

Materials and methods

An overview

This thesis is based on four questionnaire studies in three different study populations (Table 1).

Table 1. Questionnaire studies included in the thesis

Study population	Swedish Society for Coeliacs	Health on Equal terms[a]	Health economics within ETICS[b]	
Responders	Adults 20 years or older with celiac disease	Adults and adolescents 16-84 years of age	Children in 6th grade	Parents to children in 6th grade
Invited	1,560	37,912	10,041	
Study year	2009	2006	2005-2006	
Paper	I & II	II	III	III & IV
Administrative unit	Swedish Society for Coeliacs	Statistics Sweden	Epidemiology and Global Health, Umeå University	
Principal investigator	Epidemiology and Global Health, Umeå University	Swedish National Institute of Public Health	Epidemiology and Global Health, Umeå University	

[a] A study performed without our involvement.
[b] Exploring the Iceberg of Celiacs in Sweden, a cross-sectional study of celiac disease among Swedish children. The children were invited with informed consent from their parents.

Study design and study populations

The ETICS study

A school-based celiac disease screening study called Exploring the Iceberg of Celiacs in Sweden, or ETICS, was planned and performed in two phases during 2005-2006 [46], and 2009-2010. The screening phases were similar, and prevalence comparisons between phases were based on the same study design. The ETICS study was initiated as a consequence of the Swedish epidemic of celiac disease in children below two years of age [49]. The primary objective was to determine if there is a difference in total prevalence of celiac disease at 12 years of age between a cohort of children born during the epidemic years and a cohort born after the epidemic years (cohorts that differ with respect to infant feeding). A difference in prevalence between the birth cohorts has previously been shown for cases found within clinical praxis before 2 years of age and also at older ages [49,59]. It was hypothesized that a difference in the true prevalence at 12 years of age would imply that infant feeding practices could prevent children from getting celiac disease up to this age.

Children in the 6th grade from five study sites (Umeå, Norrtälje, Norrköping, Växjö and Lund) were invited to participate in the ETICS study

with the informed consent of their parents. Participating children were asked to give a blood sample at school, and it was analyzed for serological markers indicative of celiac disease. Children with positive serology were contacted by the pediatric clinic at their study site and were given information and a small intestinal biopsy was recommended [46]. For a celiac disease diagnosis, Marsh 2-3 was required or Marsh 1 and symptoms or signs indicative of celiac disease with a clinical response to a gluten-free diet [19].

In the first screening phase (the cohort born during the epidemic years) 10,041 children were invited and 7,567 participated. The prevalence of celiac disease was 3% [19,46].

In ETICS there were also two secondary objectives: i) to evaluate if a mass screening should be implemented for celiac disease, and ii) to determine if the amount of gluten during infancy and the duration of exposure are related to the occurrence of other auto-immune diseases. These objectives were investigated with different tools, among them: a) questionnaires answered by the children and their parents, b) narrative stories about participating in a screening by the children, c) focus groups with children diagnosed with celiac disease detected within ETICS and their parents, and d) analyses of blood samples regarding not only celiac disease but also other immune-mediated diseases.

Questionnaire study - Swedish Society for Coeliacs (Papers I & II)

As part of the secondary objective of ETICS regarding the evaluation of a celiac disease mass screening, a questionnaire study including adults with celiac disease was initiated. The study in itself was independent of ETICS but will contribute to the evaluation of a celiac disease mass screening, which is among the secondary objectives of ETICS.

The questionnaire study was performed in collaboration with the Swedish Society for Coeliacs, which includes patients in Sweden with celiac disease, lactose intolerance, cow's-milk protein intolerance and soya intolerance. When joining the Society, members report their year of birth, sex and food intolerances. None of this information is verified through medical registers, and the member register also lacks information about the year of celiac disease diagnosis. Based on information from Ludvigsson and colleagues, who studied biopsy information from all Swedish pathology departments in the time span 1969 to 2008 [206], we believe it is likely that 60% of the patients in Sweden with celiac disease are members of the Society [Paper II].

In May 2009, a random sample of members of the Society was invited to respond to a questionnaire. We invited members registered as having celiac disease in the Society's member register on April 1, 2009. On that day 16,478 of the 24,494 members were registered as having celiac disease. Our interest was in the 11,094 members with celiac disease who were at least 20 years of age during 2009.

In the register, 74% of the members were females and the largest numbers of adult members were in the age strata 20-24, 60-64 and 65-69 (Table 2).

Notably, members in the age stratum 20-24 were the only ones in our study sample who were born during the epidemic years, and the high proportion of members in this strata is in line with the high incidence of celiac disease for that birth cohort at age below 2 years [49]. Further, the twofold higher number of females than males in this age stratum is in line with published results [207], as is the greater number of females than males in all age strata [21]. The larger representation of persons aged 60-69 in the register is not as straightforward in relation to previous studies.

Table 2. Numbers of adult members in the Swedish Society of Coeliacs with celiac disease on April 1, 2009, according to age (in years) and sex

	Males		Females	
Age group	**n**	**%[a]**	**n**	**%[a]**
20-24	410	14	881	11
25-29	144	5.0	517	6.3
30-34	154	5.4	545	6.6
35-39	196	6.9	810	9.8
40-44	168	5.9	627	7.6
45-49	168	5.9	598	7.3
50-54	181	6.3	648	7.9
55-59	223	7.8	692	8.4
60-64	321	11	932	11
65-69	345	12	887	11
70-74	264	9.2	536	6.5
≥ 75	282	10	565	6.9
Total	**2,856**	**26[b]**	**8,238**	**74[b]**

[a] Percentage of members in each age group for males and females.
[b] Percentage of males and females within the Society.

The sampling procedure was chosen for the main purpose of predicting HRQoL throughout lifetime after a potential celiac disease mass screening. To have consistent age- and sex-based estimates we therefore chose age strata of equal size despite different distributions of members in the strata within the society. We invited 65 members in twelve five-year intervals from 20 years of age (20-24, 25-29, ..., 70-74, ≥ 75) for both males and females. A 16-page questionnaire was sent to invited members via the postal service along with a prepaid envelope to facilitate responding, and when needed three reminders were sent. An English translation of the questionnaire is available at Biomed Central [208]. The Swedish Society for Coeliacs administered the study. Microsoft Access was used for data handling. Questionnaires were scanned and thereafter checked for inconsistencies. The study was approved by the Regional Ethical Review Board at Umeå University.

Of 1,560 invited members, 1,122 responded. In the questionnaire, the responder gave information about age, sex and celiac disease diagnosis.

Questionnaires were excluded if celiac disease diagnosis determined by a health professional could not be verified, or the information about age and sex was not consistent with the member register. There were 91 questionnaires excluded, representing three groups, based on questionnaire responses: i) no celiac disease diagnosis (n=34), ii) celiac disease diagnosis uncertain (n=33), and iii) age and/or sex not consistent based on register information and questionnaire response (n=24). In group i) the responder stated no celiac disease diagnosis, while in group ii) either a self-diagnosis or no recommendation for a gluten-free diet by a medical professional was stated. The questionnaire data do not confirm the celiac disease diagnosis, but at least the exclusion criteria make the data more solid. It was important to exclude respondents who believed they had celiac disease without being diagnosed, as health improvement following gluten withdrawal can be due to other reasons, such as wheat allergy [209].

There were 1,031 (66%) eligible responders, 52% of whom were females, and the mean age was 52 years. The response rate differed between age groups and sex; 70-74-year-old males had the highest response rate and 20-24-year-old males had the lowest response rate. The overall response rate was higher among females (69%) than males (63%) (Table 3).

Table 3. Response rates among adult members of the Swedish Society for Coeliacs divided according to age and sex

	Males		Females		All	
	n	%[a]	n	%[a]	n	%[a]
20-24	30	46	41	63	71	55
25-29	38	58	44	68	82	63
30-34	33	51	37	57	70	54
35-39	32	49	43	66	75	58
40-44	35	54	42	65	77	59
45-49	32	49	40	62	72	55
50-54	39	60	51	78	90	69
55-59	50	77	44	68	94	72
60-64	48	74	49	75	97	75
65-69	53	82	47	72	100	77
70-74	56	86	54	83	110	85
≥ 75	49	75	44	68	93	72
Total	**495**	**63**	**536**	**69**	**1,031**	**66**

[a] Response rates for invited members of each group.

In Paper I we used questions covering self-reported symptoms, health care consumption, and self-reported diseases. In Paper II we used questions covering delay to celiac disease diagnosis, compliance with a gluten-free diet and HRQoL. In the sections covering self-reported symptoms, health care consumption and health-related quality of life, respondents were asked about the situation the year prior to diagnosis and initiated treatment with a

gluten-free diet, which we refer to as *pre-treatment*, and the situation the year prior to responding to the questionnaire, which we refer to as *today*. Parts of the questionnaire are planned to be used in future studies.

Health on Equal Terms (Paper II)

Since 2004 the Swedish National Institute of Public Health has conducted the Swedish national public health survey entitled "Health on Equal Terms" [210]. The survey is administered by Statistics Sweden and distributed by postal service with a prepaid envelope to facilitate responding, with three reminders when needed. The study was performed without our involvement, but we received permission to use material from the Swedish National Institute of Public Health. "Health on Equal Terms" is approved by the ethical review board at the Swedish National Board of Health and Welfare.

The aim of the survey is to measure the health of the Swedish population and to follow it over time. Every year, 20,000 citizens, ages 16-84 years, are randomly chosen to respond to 75 questions. Each county is offered the chance to extend the size of the invited sample. During 2006, the four most northern Swedish counties (Norrbotten, Västerbotten, Jämtland and Västernorrland) added the EQ-5D descriptive system (excluding EQ VAS) to the questionnaire, and they also increased the sample size.

Our only interest in the survey was the results from the EQ-5D, which have not been published elsewhere. These responses are used as reference material for our adult celiac disease patients. Characteristics, sample procedure and handling of response data from the national sample from the "Health on Equal Terms" survey during 2006 are available at the Swedish National Institute of Public Health [211], where results from the survey are presented [210].

In the four northern Swedish counties, the population during 2006 included 677,777 persons 20 years or older. For ages 16-84 years, 37,912 persons were randomly selected in strata of age, sex, county and municipality. In all, 27,809 (73%) responded to the questionnaire, with 25,797 aged 20 years or older. Females comprised 53% (n=13,781) of the responders and the mean age was 52 years, thus similar to the adult celiac disease population.

Health economics within ETICS (Papers III & IV)

In ETICS, a questionnaire to be completed in class was handed to the child after blood sampling. The child was also given a questionnaire for his/her parents, along with a prepaid envelope, to be filled in at home before being informed about the screening results. If needed, parents were reminded three times by email, postal service and/or telephone. The questionnaire was answered by either one of the parents or both of them together.

There were 7,218 children (95% of participating children) who responded to the questionnaire, and 6,524 parents (parents of 86% of participating children). The EQ-5D instrument was included in both questionnaires and

used for Paper III, while the section about WTP in the parent questionnaire was used for Paper IV. In Paper IV, 6,352 questionnaires fulfilled inclusion criteria, with questionnaires from 59 parents of children with a previous celiac disease diagnosis excluded, as well as from 113 parents who responded after being informed about the results of the serological tests.

Derived variables and statistical analysis

Paper I

In the questionnaire, symptoms were listed as *pre-treatment* and *today* with five possible answers. In analyses, responses were dichotomized to major ("often" and "always") and to minor severity ("never, "rarely" and "sometimes"). Respondents were asked for number of hospitalization days, health care visits and missed working days both *pre-treatment* and *today*. Comparisons were also done between *pre-treatment* and *today* for screening-detected celiac disease, and recently diagnosed celiac disease. We defined members as screening-detected celiac disease cases if they responded that their primary investigation for celiac disease was started based only on other disease and/or due to a family member with celiac disease, while other cases were defined as clinically-detected cases. Recently diagnosed celiac disease was defined as having a diagnosis between 2005 and 2009. All comparisons between *pre-treatment* and *today* were done with the sign-test. Comparisons between screening-detected celiac disease and clinically-detected celiac disease, as well as comparisons between recently diagnosed celiac disease and others with the year of celiac disease diagnosis specified, were done using Student's t-test.

The appearance of other diseases was noted by the respondent, and the year of diagnosis was stated. For each of the diseases the proportion of diagnoses after the celiac disease diagnosis was compared with the proportion of diagnoses during the same year or prior to the celiac disease diagnosis using Student's t-test. Comparisons were done based on the hypothesis that fewer diagnoses after having a celiac disease diagnosis indicates a preventive effect from a gluten-free diet for immune-mediated disease. Responders reported whether they had stopped taking any drug, and if so the name of the drug(s), after their celiac disease diagnosis.

Population means were calculated based on average within population and not by stratified means. A statistical significance level of 5% was used. Analyses were performed, and graphs were created, with Stata 11.2 (Stata-Corp LP, College Station, TX).

Paper II

To measure delay to the celiac disease diagnosis, adult respondents were asked about the year of their first symptoms indicative of celiac disease, the year of their first visit to a doctor due to symptoms indicative of celiac disease, and the year of celiac disease diagnosis. The delay from first symptoms indicative of celiac disease to diagnosis was estimated as

difference in years to diagnosis with 0 years if no symptoms were reported prior to the celiac disease diagnosis. The delay from first doctor visit due to symptoms indicative of celiac disease was estimated similarly. Delays were also analyzed in age at diagnosis groups, which consisted of both the same age intervals as for the age strata of invited members (20-24, 25-29, …, 70-74, ≥75), and age strata for ages below 20 years (0-4, 5-9, 10-14 and 15-19). Additionally, the Cox proportional hazards model was used to study if the delay had changed over time [212]. If the exponential of the hazard ratio is above 1 this implies a shorter delay from first symptoms indicative of celiac disease diagnosis to diagnosis compared to the baseline, which was a diagnosis before 1980.

The Swedish translation of EQ-5D was used to measure HRQoL [173], with the design, adapted from Gray and Papanicolas [30], intended to measure both *pre-treatment* and *today* for the adult celiac disease population. Responses to the EQ-5D descriptive system were translated to QALYs using the UK weights [170]. Differences in QALY between *pre-treatment* and *today*, as well as between *today* and the general population, were compared with Student's t-test. The effects on HRQoL by sex, age and delay in diagnosis were analyzed with linear regression analysis.

Population means were calculated based on average within population and not stratified means. A statistical significance level of 5% was used. Analyses were performed, and graphs were created, with Stata 11.2 (Stata-Corp LP, College Station, TX).

Paper III

To measure HRQoL, a Swedish child-friendly pilot version of EQ-5D was used in the child questionnaire. It was developed by Burström and colleagues and has been shown to be valid for a Swedish child population [213,214]. The version was developed from the Swedish translation of EQ-5D, also using the English child-friendly EQ-5D version EQ-5D-Y in the translation process [215]. The five dimensions of the child-friendly version correspond to mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried or sad, and the severity levels are "no problems", "some problems" and "a lot of problems/unable" [213,214]. For the parent questionnaire, a standard proxy version of the Swedish EQ-5D adult version was used, where parents were asked how they would rate their child's health [169]. For the child questionnaire, responses to the five EQ-5D dimensions were dichotomized to "no problems" and "problems", where the latter included both "some problems" and "a lot of problems/unable", for comparisons between groups. The responses from their parents were treated similarly.

The groups used in the paper were defined as follows:

- Screening-detected celiac disease: positive serology and biopsy-proven diagnosis
- No celiac disease: not diagnosed with celiac disease prior to the study and negative serology
- Previous celiac disease: celiac disease marked in informed consent for study participation and diagnosis confirmed through medical records

For these groups, comparisons were done for the EQ-5D dimensions with Fisher's exact test, and for EQ VAS with the independent samples median test. Comparisons between boys' and girls' responses were done with the Mann-Whitney U test.

A statistical significance level of 5% was used. Analyses were performed with SPSS 17 (SPSS Inc., Chicago, IL).

Paper IV

To measure WTP, the child's parents had a scenario in their questionnaire where the concept of screening was introduced and the implications of a celiac disease diagnosis of their child was explained with respect to health risks and treatment options. An English translation of the scenario is available in Figure 1 in Paper IV. Based on the scenario, parents first responded as to whether or not they would be willing to pay something for having information about the celiac disease status of their child. If they were willing to pay they were asked to state their WTP in SEK (10 SEK ≈ 1 EUR), and if not they were asked for their reason.

Only responses with either "yes" or "no" to the willing to pay question were used to calculate the proportion of parents willing to pay anything for a screening. The WTP of parents was estimated based on two approaches. In the conventional WTP approach only those who were willing to pay and stated an amount of more than 0 SEK, and those who were not willing to pay and either stated an amount of 0 SEK or no amount, were included in the analysis. A rather high percentage (19%) of parents responded with a text string instead of stating an amount. In the inclusive WTP approach, these responses were included if they stated a valid WTP (see decision rule in Table 2 of Paper IV). The inclusive approach also included those who failed to respond as to whether they were willing to pay or not if they stated a valid WTP. For the inclusive approach all who responded that they were not willing to pay for a celiac disease screening were included with a WTP of 0 SEK. The main WTP approach used was the inclusive approach, and sub-analyses were only presented for this approach. WTP is commonly presented in studies as mean WTP. In our case the distribution of the WTP responses is heavily skewed and the median is therefore also presented.

The WTP was compared with the average cost per child for a celiac disease screening. For a range of cost items, estimates were derived based on information from the health care divisions of the Västerbotten and Östergötland county councils in Sweden, and from the first screening phase of the ETICS study. Cost items are listed below:

- Blood sampling at school (including nurses' salaries and material)
- Analyses of serological markers
- Small intestinal biopsy (including gastroscopy and pathological anatomic evaluation)
- A visit to a physician
- A visit to a dietician

Determinants for parents' WTP were analyzed with interval regression [216]. The investigated determinants were parental education, household income, celiac disease in the family, the health of the child with respect to well-being, other self-reported diseases for the child, and problems with symptoms.

A statistical significance level of 5% was used. Analyses were performed with Stata 11.2 (Stata-Corp LP, College Station, TX).

Main results

The burden of living with untreated celiac disease (Papers I & II)

A majority of responders reported major problems *pre-treatment* (Table 4). Most common were flatulence (64%), fatigue (62%), soft stool (54%) and abdominal pain (53%).

Major problems with abdominal pain, flatulence, soft stool, fatigue, weight loss and vomiting were less frequently reported *pre-treatment* by screening-detected celiac disease cases than by clinically-detected cases (Table 4). Despite being less frequent, the first four symptoms were still the most frequently reported symptoms in this subgroup. Those recently diagnosed (2005-2009) reported a similar extent of problems for all symptoms *pre-treatment*, but they reported fewer problems with weight loss (28%), vomiting (3%) and mouth ulcer (7%), compared to those with an older diagnosis.

Table 4. Major symptoms *pre-treatment*

	All[a] (n=1,031)		Screening-detected[b] (n=180)	
Symptom	**n[c]**	**%**	**n[c]**	**%**
Abdominal pain	486	53	60	38[§]
Flatulence	573	64	74	49[§]
Hard stool	171	19	30	20
Soft stool	503	54	63	39[§]
Fatigue	578	62	86	53[§]
Weight loss	364	40	33	21[§]
Mood swings	214	24	34	21
Depression	240	26	37	23
Headache	152	17	26	16
Joint pain	141	16	23	14
Body pain	139	15	26	16
Heartburn	200	22	35	22
Nausea	136	15	18	11
Vomiting	70	8	4	3[§]
Skin rash	135	15	23	14
Mouth ulcer	84	9	17	11
Hair loss	37	4	5	3

[a] There were 879-918 who responded to each of the symptoms both *pre-treatment* and *today*.
[b] Primary investigation started based on a disease with known relation to celiac disease or due to heredity for celiac disease, with 151-162 responding to each of the symptoms both *pre-treatment* and *today*.
[c] Patients responding to having problems "Often" or "Always".
[§] Significant difference between screening-detected and clinically detected cases using Student's t test.

Celiac disease patients, both males and females, reported a lower QALY *pre-treatment* than a general population (Table 5). Females, both the celiac disease patients *pre-treatment* and the general population, reported a lower QALY than males, with a bigger difference in celiac disease patients. Also, on the EQ VAS a worse HRQoL was reported for females than males *pre-treatment* (Table 5). Besides sex (females having worse QALY), the factors negatively affecting QALY *pre-treatment* were a younger current age, a delay in celiac disease diagnosis (two years or longer delay in getting a celiac disease diagnosis from first symptoms indicative of the disease), and a celiac disease diagnosis before 1990 compared to more recently (1990-2004). For all factors the p-value was below 0.01.

Table 5. Quality-adjusted life year (QALY) scores and EQ VAS *pre-treatment* for adults with celiac disease and QALY scores for the general population

	Celiac disease[a]				General population[a]	
	QALY[b]		EQ VAS		QALY[b]	
	n	Mean	n	Mean	n	Mean
Males	393	0.71	437	52	11,428	0.81
Females	386	0.60	477	44	13,032	0.77
All	**779**	**0.66**	**914**	**48**	**24,460**	**0.79**

[a] Responded to all dimensions both *pre-treatment* and *today*.
[b] QALY scores were calculated from responses on the EQ-5D descriptive system

Delay to celiac disease diagnosis (Paper II)

The mean delay from first symptoms indicative of celiac disease to diagnosis was 9.7 years with a median delay of 4 years (quartiles 1-14 years). The mean delay from first symptoms to diagnosis was at least 6 years for all age-at-diagnosis groups above 19 years. The mean delay from first doctor visit due to possible celiac disease-related problems to diagnosis was 5.8 years with a median delay of 1 year (quartiles 0-8 years).

The median delay from first symptoms indicative of celiac disease to a diagnosis has increased during recent decades. However, at the same time the age at diagnosis has increased: from a mean age of 17 years (median 2 years) at diagnosis before 1980, to 27 years (median 32 years) for 1980-1989, to 45 years (median 46 years) nowadays, i.e. 2005-2009. The increase in the delay to diagnosis from first symptoms can only be explained by the increased age at diagnosis during recent decades. In fact, the trend is a decreased delay over time for age-at-diagnosis groups (Figure 2), with a significant decrease detected for those diagnosed before 1990 when compared with those diagnosed in 2000-2004 for males and females aged 20-39, and females aged 40-59. For females aged 20-39 there was also a significant decrease in delay when comparing those diagnosed before 1990

with those diagnosed in 1990-1999. No significant decrease in delay was observed for those diagnosed most recently (2005-2009) compared with those diagnosed before 1990.

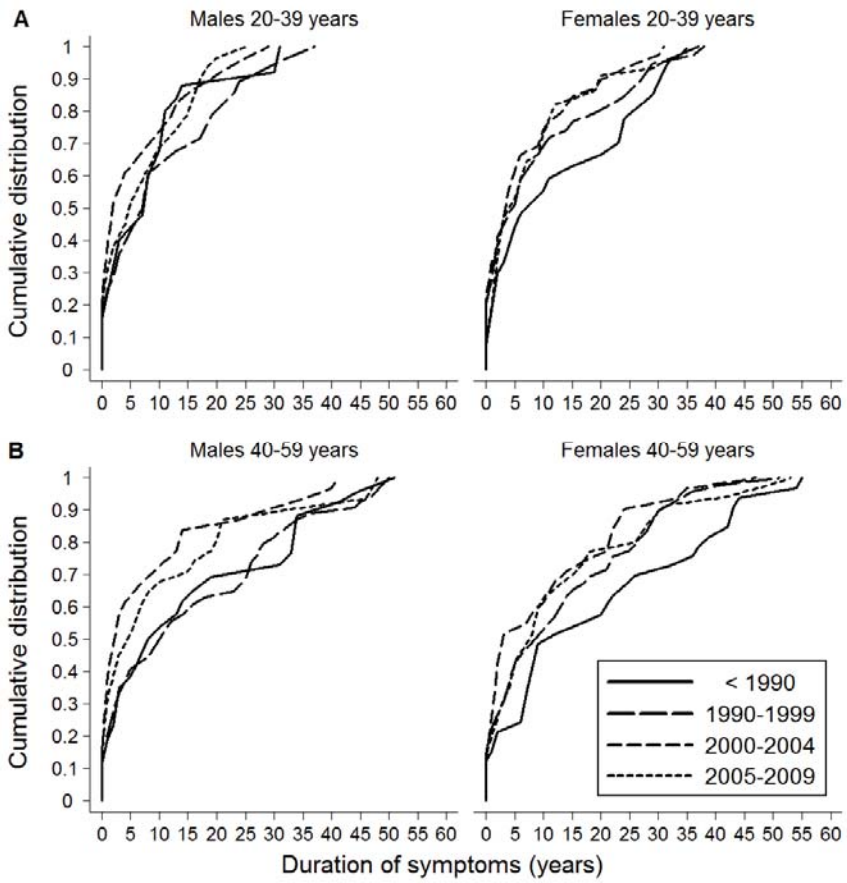

Figure 2. Delay to celiac disease diagnosis from first symptoms indicative of the disease. The delay is shown in groups formed by decade for diagnosis, sex and age at diagnosis (A) 20 to 39 years and (B) 40 to 59 years.

Health improvement from a gluten-free diet (Papers I & II)

After celiac disease diagnosis and initiated treatment with a gluten-free diet most symptoms were improved, both when considering all cases, where only joint pain did not improve, and screening-detected cases, where joint pain, body pain, vomiting, skin rash and hair loss did not improve (Table 6). None of these symptoms were frequent (at most reported by 16%) *pre-treatment*. For recently diagnosed (2005-2009) cases there was an improvement after diagnosis for all symptoms except vomiting and hair loss, both a small problem *pre-treatment* with at most 3% reporting major problems.

Table 6. Proportion of celiac disease patients with major symptoms after initiated treatment with a gluten-free diet

	All[a] (n=1,031)			Screening-detected[b] (n=180)		
Symptom	**n[c]**	**%**	**Reduction[d]**	**n[c]**	**%**	**Reduction[d]**
Abdominal pain	81	9	44*	8	5	33*
Flatulence	189	21	43*	22	14	35*
Hard stool	95	11	8*	18	12	8*
Soft stool	130	14	40*	18	11	28*
Fatigue	202	22	40*	43	27	26*
Weight loss	35	4	36*	5	3	18*
Mood swings	56	6	18*	8	5	16*
Depression	63	7	19*	12	7	16*
Headache	77	9	8*	12	7	9*
Joint pain	126	14	2	22	14	0
Body pain	105	12	3*	18	11	5
Heartburn	51	6	16*	7	4	18*
Nausea	26	3	12*	2	1	10*
Vomiting	8	1	7*	1	0.6	2
Skin rash	74	8	7*	15	9	5
Mouth ulcer	21	2	7*	3	2	9*
Hair loss	20	2	2*	2	1	2

[a] There were 879-918 who responded to each of the symptoms both *pre-treatment* and *today*.
[b] Primary investigation started based on a disease with known relation to celiac disease or due to heredity for celiac disease, with 151-162 responding to each of the symptoms both *pre-treatment* and *today*.
[c] Patients reporting problems "Often" or "Always".
[d] Reduction in proportion of celiac disease patients with major symptoms in absolute percentage between *pre-treatment* and *today*.
* Statistically significant reduction in symptoms using Student's t-test.

HRQoL improved after diagnosis and was even slightly higher than for the general population. EQ VAS also improved after a diagnosis. The pattern was similar for both males and females. The QALY gap between males and females was 0.04 for both celiac disease patients *today* and the general population (Table 7).

Table 7. Quality-adjusted life year (QALY) scores and EQ VAS *today* for adults with celiac disease and QALY scores for the general population

	Celiac disease[a]				General population[a]	
	QALY[b]		EQ VAS		QALY[b]	
	n	Mean	n	Mean	n	Mean
Males	393	0.88	437	83	11,428	0.81
Females	386	0.84	477	80	13,032	0.77
All	**779**	**0.86**	**914**	**81**	**24,460**	**0.79**

[a] Responded to all dimensions both *pre-treatment* and *today*.
[b] QALY scores were calculated from responses to the EQ-5D descriptive system

There was a decrease in health care consumption concerning both health care visits and hospitalization days between *pre-treatment* and *today*, and also for missed working days (Table 8). This improvement was also seen in screening-detected cases. For recently diagnosed cases (2005-2009) there were improvements *today* in health care visits and missed working days, but not hospitalization days. After getting a celiac disease diagnosis, 13% (n=136) reported that they could discontinue at least one medication.

Table 8. Health care consumption *pre-treatment* and *today*

		Pre-treatment		Today		p[a]
	n	Mean	Md[b]	Mean	Md	
All						
Health care visits	814	5.4	3	3.7	2	<0.01
Hospitalization	836	2.3	0	0.7	0	<0.01
Missed working days[c]	754	7.2	0	2.5	0	<0.01
Screening-detected[d]						
Health care visits	144	4.8	2	4.1	1	<0.01
Hospitalization	151	3.0	0	1.0	0	0.04
Missed working days[c]	136	9.0	0	1.8	0	<0.01

[a] Comparisons between *pre-treatment* and *today* using the sign-test.
[b] Median
[c] Also including missed school days and similar missed days.
[d] Primary investigation started based on a disease with known relation to celiac disease or due to heredity for celiac disease.

The most frequently reported immune-mediated diseases were thyroid disease (9.1%) and rheumatic disease (7.8%). Both diseases were more common among females (thyroid disease 14% and rheumatic disease 11%). Inflammatory bowel disease was the disease most frequently reported as diagnosed during the same year as celiac disease (27%).

For immune-mediated diseases, only vitiligo was less frequently diagnosed after celiac disease diagnosis. No relation to diagnosis of celiac disease and a supposed gluten-free diet was seen for the other immune-mediated diseases considered (diabetes, rheumatic disease, thyroid disease, alopecia areata and inflammatory bowel disease).

Health-related quality of life for children with celiac disease (Paper III)

No significant differences across the groups screening-detected celiac disease, previously diagnosed celiac disease and no celiac disease were found in any of the EQ-5D dimensions or the EQ VAS in either the child (Table 9) or the parent questionnaire. For comparisons of the boys and girls, respectively, across groups, there was only a significant difference in the dimension doing usual activities for boys in the child questionnaire.

Table 9. Children reporting problems, by EQ-5D dimensions and across groups, before the children's screening-detected celiac disease (CD) diagnosis

	Screening-detected CD[a]		Previously diagnosed CD[a]		Non-CD[a]	
Dimension	**Problems[b]**		**Problems**		**Problems**	
	n	**%**	**n**	**%**	**n**	**%**
Mobility	6	4	2	3	190	3
Looking after myself	1	1	1	2	29	1
Doing usual activities	5	3	1	2	164	2
Having pain or discomfort	32	22	9	15	1,367	20
Feeling worried or sad	20	14	8	13	785	11

[a] For each of the EQ-5D dimensions 147-148 children responded in the screening-detected CD group, 62 children responded in the previously diagnosed CD group, and 6843-6862 children responded in the non-CD group.
[b] Reporting "some problems" or "a lot of problems/unable".

Parents' valuation of a celiac disease diagnosis (Paper IV)

There were 3,809 parents willing to pay for the information provided by a celiac disease screening, corresponding to 63% of the valid responses.

Among 2,248 responders not willing to pay, the most common reason was "I do not believe our child has celiac disease" (66%).

With the inclusive approach the mean maximum WTP was 79 EUR, with a much lower median of 10 EUR. With the conventional approach the mean maximum WTP was 48 EUR, also with a much lower median of 7.2 EUR. Among parents answering with a text response instead of stating a WTP it was common to specify a fee, for example for a visit to a physician.

The cost for a celiac disease screening is specified in Table 10. The highest average cost per child for a cost item was for the analyses of serological markers (18 EUR), and gastroscopy (12 EUR). The total average cost per child for a screening was 47 EUR. This is a lower amount than the mean maximum WTP for both the inclusive and the conventional approaches, but higher than the median WTP for both approaches. Despite the high average WTP, in the inclusive approach only 23% stated a WTP of at least the average cost per child for a screening, and in the conventional approach the figure was 21%.

Table 10. Costs for a celiac disease screening of 12-year-olds in Sweden

Cost item	Cost, EUR[a]	n	Average cost per child, EUR
Blood sampling at school			7.2
Nurses' salaries	5.4	7,500	
Material	1.8	7,500	
Analyses of celiac disease serological markers			18
atTG[b]-IgA and total serum IgA	18	7,207	
EMA[c]-IgA	11	222	
atTG-IgG	20	170	
EMA-IgG	29	5	
Gastroscopy with a small intestinal biopsy and pathological anatomic evaluation			12
Gastroscopy	380	184	
Pathological anatomic evaluation	100	184	
A visit to a physician	210	192	5.4
A visit to a dietician[d]	210	145	4.1
Total	**348,803**		**47**

[a] Costs for activities were based on information from the health care divisions within the Västerbotten and Östergötland county councils in Sweden and from the ETICS screening study. Average cost per child was calculated from the actual cost for each activity divided by the 7,500 children involved, also including those (n=293) for whom blood sampling was unsuccessful.

[b] Anti-human tissue transglutaminase.

[c] Endomysial antibodies.

[d] The fee for a physician's visit was used.

Factors that increased the WTP were a higher level of education (cutoff point of at least 1 parent having >12 years' of schooling), a higher salary, and that the child had symptoms indicative of celiac disease (often or always fatigue, abdominal pain, abdominal discomfort, flatulence, hard stools, and/or soft stools).

Discussion

Main findings

Swedish adults with celiac disease retrospectively reported a high frequency of symptoms before diagnosis [Paper I]. They also reported a lower HRQoL before diagnosis compared to the general population [Paper II]. Many had to live with undiagnosed disease for a long time, as today there is still a long delay to a celiac disease diagnosis [Paper II]. After diagnosis and initiated treatment with a gluten-free diet, HRQoL improved to the level of the general population [Paper II], there was a reduction of symptoms, and health care consumption was reduced [Paper I]. A possibly positive effect of initiated treatment with a gluten-free diet was also seen in children, as children with clinically detected disease experienced a similar HRQoL as children without celiac disease [Paper III]. Screening-detected children also reported HRQoL comparable to that of children without celiac disease [Paper III]. We explored whether a gluten-free diet could reduce the risk for development of celiac disease-related immune-mediated diseases, and our results indicate that the risk reduction, if any, is likely to be small. [Paper I].

This thesis covers not only the value of having a celiac disease diagnosis in terms of health gain, but also in terms of monetary value [Paper IV]. Parents' mean WTP for having information about the celiac disease status of their child through a mass screening was higher than the average cost of a celiac disease screening. However, only a minority of the parents were willing to pay that amount.

Methodological considerations

Three independent questionnaire studies were used in this thesis, and all of them had limitations in both study design and methods, which are discussed below.

Adult celiac disease patients

We invited members in strata, and stratified estimates are therefore recommended. However, stratified estimates are also biased due to non-responses. Assuming that non-responders on average had the same opinion as responders in each stratum would nevertheless complicate estimates, as the sizes of non-responses between strata were not proportional. For simplicity, both for the reader in understanding the estimates and for calculation of the estimates, we decided to use means based on all responders and not the stratified means. To justify our decision we did validation checks and found no reason to believe that the main conclusions from the study would be affected.

There is no straightforward unbiased estimate of delay to celiac disease diagnosis. With our design, there is an obvious risk of a recall bias for the year of first symptoms indicative of celiac disease, year of first doctor visit

possibly due to celiac disease, and year of celiac disease diagnosis, which is likely to affect both the mean delay and the comparisons between delays in different time periods. I believe our design, which indirectly rather than directly asks for the delay, is preferable, as the latter design, which has been used elsewhere [30], might tempt the respondent to overestimate the length of their problems. It is important to keep in mind that the first symptoms are not necessarily due to celiac disease, and also that a person can have the disease without symptoms, both of which can affect the estimates of the delay to diagnosis. I believe that our estimate is adequate for measuring delay to celiac disease diagnosis.

We required an age of at least 20 years to be invited, and it was therefore not possible to be below 15 years of age if diagnosed between 2005 and 2009. We also faced the problem that celiac disease patients who had a diagnosis and later died were not part of the study. As a result, the median age at diagnosis is very likely underestimated for those diagnosed in 1990 or earlier and overestimated for those more recently diagnosed. Even so, the difference in median age over time was of such a size that our conclusion is still relevant. We focused our comparisons of delay over time for the age at diagnosis groups 20-39 years and 40-59 years. Few of those diagnosed in the past who would be at least 20 to 39 years of age today were likely to be dead at time of our study, implying that comparisons between time periods should be valid.

There is a risk of a recall bias and of too poor health being reported. However, there was also a significant reduction for both health care visits and missed working days for those recently diagnosed (celiac disease diagnosis between 2005 and 2009), as well as significant symptom relief for most symptoms for these patients, which supports our conclusions. Questioning patients at the time of diagnosis is likely to be a more accurate way of estimating health, despite an obvious risk that they over-report their problems, but that is both more time consuming and expensive. I believe our design is an acceptable compromise between precision and cost.

HRQoL in the celiac disease population in Sweden was compared with a general population in northern Sweden. To validate this we compared HRQoL for celiac disease patients from northern Sweden with celiac disease patients from the whole country. Since we could not detect statistically significant differences, our comparisons are likely to be valid. Responders with celiac disease and from the general population had similar age distributions (same median, mean, and third quartile, and similar first quartile), and proportions of female responses. Thus, it should be reasonable to compare the populations.

The treated celiac disease population responded with a higher QALY value than the general population. This could possibly be explained by those with celiac disease adapting to a healthier life. It could also be due to the "subjectiveness" of QALYs. This could lead, for example, to a cancer patient rating his or her health as better than a person with more trivial health problems, simply because the frame of reference differs and not because the

person actually has better health. Other measurements, such as disability-adjusted life years (DALYs) [217], try to measure HRQoL more objectively. The DALY score is assigned by a professional based on the disabilities of a patient. However, people with a disability might actually have a better life than others, so this "objective" measurement is not optimal for estimating HRQoL. I believe that QALYs are the best suited measure for our purpose.

We estimated QALY scores based on the UK tariff of the EQ-5D descriptive system [170], as there are limitations in the Swedish tariff [172,173]. This tariff has been used for the Swedish population before, including by Burström and colleagues [173], but it is probably not perfectly suited for the Swedish population, and comparisons with other populations should be done with caution. For comparisons within the Swedish population our results should most likely be valid.

Our design is weak for the purpose of studying the relation with other immune-mediated diseases, and we cannot determine the causal relation with certainty. We do, however, believe that the recall bias should be low, as the respondent is likely to remember which disease was diagnosed first. A more advanced design is required to study the effect of a gluten-free diet. Such a design would need to consider factors such as median/mean age at the time of having both diseases diagnosed, and the extent of gluten exposure for both treated and untreated celiac disease patients. A randomized trial with a treated and untreated group might be the best alternative for evaluating the causal link, but it is not doable for ethical reasons.

We did not invite non-members of the Swedish Society for Coeliacs as this would have required resources we do not consider justified. Our sample, without non-members and non-responders, is likely to correspond to about 40% of the adult celiac disease population in Sweden. We consider our results important even if they are only valid for responders, as they show that the experienced burden of celiac disease is large for a population of considerable size.

HRQoL in children

A similar HRQoL was reported by both the child and their parent for children with celiac disease diagnosed in ETICS and for other children. This might be due to them actually experiencing the same HRQoL, i.e. health at 12 years of age might not be affected by untreated celiac disease. However, it might also be explained by the EQ-5D instrument possibly not being sensitive enough to capture small health differences across groups, or that children who got diagnosed in ETICS are overrating their health due to poor knowledge about the "healthy" state. In fact, in focus group discussions at a follow-up of children who got diagnosed in ETICS, some children and parents retrospectively recognized that they previously had health problems [218], which indicates that the latter statement might be correct. A retrospective design at the time of diagnosis has its advantages, but I still believe that HRQoL is rated better with a prospective design.

How parents rate their WTP

Parents were handed a scenario based on which they were asked to value information about celiac disease status, but not the life-long perspective, and their WTP was therefore only compared with the screening-related costs. Possibly the long-term benefits of a diagnosis were also valued by the respondents, and the WTP therefore overestimated. There is a limit to how much detail can be used to describe a scenario. A too detailed scenario might overload the respondent with information, and because of that nothing was mentioned about asymptomatic celiac disease. Limiting information in the scenario can lead to a hypothetical bias of the WTP [176].

Most (95%) marked either "yes" or "no" to the willing to pay question, and the proportion of "yes" responses among them should therefore be a valid estimate. In Sweden, child health care is free of charge, and income taxes are higher than in most other countries. Parents were told "think of a situation where the only way to find out if your child has gluten intolerance is that your household pays for it". Despite this information, they might dislike paying a fee due to tax issues, which was also indicated in text responses to the WTP question. Some parents might even believe that the questionnaire could be used as a tool for price-setting a future screening. These arguments are likely to affect parents' WTP negatively.

A high proportion (43% of valid responses) of sent-in questionnaires did not state a WTP, and the WTP was also quite often (18% of valid responses) given along with a text, e.g. "patient fee" and "cost does not matter". Instead of removing all text responses, and as we could not find recommendations on how to handle them in the literature, we created the so-called inclusive approach in which some (n=389) of them were included. Only a small proportion (about 135 responses) of excluded responses indicated an ability to decide on a WTP level, and a high WTP was indicated among them, as a very high WTP often was mentioned. Being asked to value anything by stating WTP without being given alternatives for which to use resources, e.g. a diabetes screening or even a new sports centre, tends to inflate the valuation [219]. It is therefore likely that parents overstated their WTP. A source that likely underestimates the WTP is the open-ended format [177]. I am not able to determine the direction of the potential bias of our WTP from the reasons above, including the effect of non-response to the question and questionnaire.

Despite the weaknesses of the WTP approach [219], including all potential biases, it is still likely to be the best option for measuring the absolute benefit of a celiac disease mass screening in monetary terms.

Health before celiac disease diagnosis

It is difficult to compare the extent of reported symptoms in our study with that in other studies [Paper I]. To my knowledge the only similar study that retrospectively reported symptoms *pre-treatment* was conducted on members of Coeliac UK, and that study also reported a high burden of symptoms [30].

In a celiac disease mass screening in the United States a similar extent of symptoms was prospectively reported by adults with undetected celiac disease and adults without celiac disease [220], which is in line with the HRQoL of children in our study [Paper III]. It could be similarly argued that adults with unrecognized celiac disease might have underreported their symptoms. Even so, this study indicates that those with unrecognized celiac disease do not have pronounced symptoms. In our screening-detected group of adults only three responders were identified as mass screened [Paper I], and the fact that we found a large number of retrospectively reported symptoms *pre-treatment* indicates that screening-detected cases from risk groups might have poorer health than mass screened cases.

Our design of the EQ-5D instrument in Paper II was adapted from a previously mentioned UK study [30]. Both studies revealed a lower HRQoL *pre-treatment* than in the general population. They considered their HRQoL *pre-treatment* as similar to that of stroke patients, which illustrates the extent of problems that celiac disease patients in the UK retrospectively reported. One promising finding in Paper II is that HRQoL has improved for those recently diagnosed. However, their HRQoL is poor.

Improvements in health following a celiac disease diagnosis

We report that a gluten-free diet has a positive effect on symptoms for adults with celiac disease [Paper I], as did a Finnish study [221]. Both studies show the same effect for screening-detected cases from risk groups. Our study [Paper II], and the study by Grey and Papanicolas in the UK, both retrospectively report an improvement in HRQoL to the level of the general population after diagnosis and initiated treatment with a gluten-free diet [30]. This is also supported by a Spanish study where newly diagnosed adults on a normal diet were compared with patients on a gluten-free diet [185], and a Dutch screening study of 2-4-year-olds [190]. We also found a positive effect from gluten withdrawal on HRQoL for children with celiac disease, which is supported by other studies [188,222].

A lower HRQoL for adult females than adult males with celiac disease has been reported [223], and is supported by us [Paper II]. However, this was also the case for the general population and might not specifically be the case for celiac disease [Paper II]. Studies have shown that high compliance with a gluten-free diet might improve HRQoL [182,185,191]. We reported a very high compliance rate (96%) [Paper II], but the health benefits might be different in countries with lower compliance.

A relation to other immune-mediated diseases has been shown [61,73], and a preventive effect of gluten withdrawal on their development has been suggested but not well confirmed [61,135-137]. A clear positive effect has only been shown for dermatitis herpetiformis, also considered a skin manifestation of celiac disease [93]. We observed a lower rate of vitiligo diagnoses after celiac disease diagnosis [Paper I], which is in line with a case report [145], but more studies are required to verify such a link. Our data are weak but indicate that a celiac disease diagnosis with a following gluten withdrawal is not likely to have a pronounced impact on the risk of developing other immune-mediated diseases such as diabetes mellitus type 1 and thyroid diseases.

The difficulties in receiving a celiac disease diagnosis

In our study the delay from first symptoms of celiac disease to diagnosis was 10 years [Paper II]. Other studies measuring this delay have shown both longer delays, 11-13 years in the United States [31], UK [30], and Canada [29], and shorter delays of 4-6 years in Italy [32], Germany [33], and the United States [9,34]. In most studies reporting a shorter delay, the design differs a great deal from ours. Some include patients with a more recent diagnosis, and some estimate the delay from information in patient files, making it more similar to the delay from first doctor visit due to symptoms. Our results seem to be in good accord with those of others, and the delay in diagnosis seems to be a worldwide problem.

We reported a decrease in delay during recent decades [Paper II], which is in line with other studies [9,30]. However, we showed that many people still have to wait a long time for a diagnosis, e.g. around 50% of those aged 20-39 years, and diagnosed between 2005 and 2009, had to wait for 5 years or more for a diagnosis. Similar to our study [Paper II], others have reported an increasing age at diagnosis during recent decades [9,11,12]. It is important to shorten the delay, as this likely would lead to health gains as well as health care savings [Paper I & Paper II].

Awareness and knowledge about celiac disease have increased over time. In the past, celiac disease was defined as a rare childhood disease; nowadays it is considered a rather common disease that can occur at any age. Improvements in diagnostic facilities have helped in the recognition of new cases, and both the small intestinal biopsy and serology tests have led to gradual improvement in detecting the disease [15,17,27,28].

Over time it has become apparent that a large proportion of celiac disease patients do not have classical symptoms, and the presence of only atypical symptoms at the time of diagnosis has increased as a consequence [9]. In a study in the UK, the delay to celiac disease diagnosis was investigated from the first appearance of a symptom, and although anemia, which is well known to be related to celiac disease [111], was one of the most commonly reported symptoms (65%), the delay to diagnosis with that symptom was the second longest (11.5 years) for any symptom [30]. All other symptoms with a longer delay than 10 years are also referred to as atypical (mouth ulcer,

headache and constipation). It would have been valuable to study the first appearance of a symptom in Swedish adults with celiac disease.

It was concluded in a study from the United States that the lack of awareness of celiac disease among primary care physicians contributes to under-diagnosis of the disease [224]. Interestingly, only 45% of the physicians were aware that anemia was associated with celiac disease, and only 35% of the primary care physicians had ever diagnosed someone with celiac disease. A similar lack of awareness was also shown in the UK. Based on a case description consistent with celiac disease, a majority of doctors (60%) failed to link the description to the disease [225]. Interestingly, and consistent with the two previously mentioned studies [30,224], anemia was the cue that most doctors failed to link to celiac disease. Awareness of the disease might be better in Sweden. However, since the delay in Sweden [Paper II] is similar to the delay in the United States and the UK [30,31], it is likely that awareness among Swedish physicians also needs improvement.

Economics in celiac disease

The economic aspects of living with both treated and untreated celiac disease have received little study. We found a reduction in health care consumption after initiated treatment for celiac disease, which implies a cost reduction for the health care sector [Paper I]. This is in line with the health improvements in terms of HRQoL and symptoms that we also reported [Paper I & Paper II]. Interestingly, it has been shown that Swedish females with treated celiac disease use health care more than other Swedish females [205], which implies higher costs. We lack information about health care use for Swedish females in the general population, and could therefore not make any comparison [Paper I]. In the United States it was recently estimated that a celiac disease diagnosis reduced medical costs by $1,764 compared to the year preceding the diagnosis [204]. This is in good agreement with our findings [Paper I].

The only two previous health economic evaluations of a celiac disease mass screening are from the same research team [194,195]. They concluded that a mass screening is cost-effective, based on certain assumptions that still need to be validated. Both evaluations lack complete coverage of future costs and savings from a screening. We have performed the first cost-benefit analysis of a celiac disease mass screening, and the first estimate of the cost for a school-based screening [Paper IV]. Our study confirms an interest among parents to pay for being informed about their child's celiac disease status.

Should we screen everyone for celiac disease?

Currently, case finding is frequently carried out in risk groups, even if symptoms indicative of celiac disease are lacking. Among common risk groups are first-degree relatives, diabetes mellitus type 1 patients, autoimmune thyroid disease patients and Down syndrome patients [22]. An increased awareness among physicians is likely to improve the detection rate of celiac disease through case finding, but will not detect patients outside of risk groups. The first symptoms indicative of celiac disease have been shown, both by us [Paper II], and others [33], to occur some years before the first meeting with a physician, implying that increased awareness in the general public is also important.

An alternative to case finding is celiac disease mass screening. Both unrecognized cases, due to lack of awareness on the part of the physician and/or affected patients themselves, as well as asymptomatic patients, will then be detected. There has been debate in recent decades as to whether a celiac disease mass screening should be implemented [156-163,165]. More information is requested by most researchers before recommendations on whether and when to perform a mass screening [160-163].

Principles of Wilson and Jungner for celiac disease mass screening

The principles proposed back in 1968 by Wilson and Jungner are still used as guidelines for discussions on a mass screening [155]. The principles for mass screening in relation to celiac disease are discussed below, and at the end of each section the number of the principle is given in brackets. See "*Suggested principles*" section for numbering of principles.

Celiac disease can be considered an important health problem as it has a high prevalence for a chronic disease (estimated at 1% in the Western World [45]), and undiagnosed the disease is associated with a poor HRQoL (reported by us [Paper II] and others [30,185]), a high prevalence of symptoms (reported by us [Paper I] and others [30,221]), and an increased use of health care facilities (reported by us [Paper I] and others [204]). Celiac disease is also believed to be related to an increased risk for immune-mediated diseases [61,162] and a shortened life length [122]. [Principle 1]

It is commonly agreed that celiac disease has a recognizable latent and early symptomatic stage, but its natural history is not fully understood. For clinically detected cases a diagnosis seems beneficial in many respects, e.g. a health gain from gluten withdrawal in terms of symptom relief (reported by us [Paper I] and others [221]), improved HRQoL (reported by us [Paper II] and others [30,185,190]), and a positive effect on dermatitis herpetiformis and bone-related problems [93,147]. Gluten withdrawal might also protect against the appearance of immune-mediated diseases [61,135,136], and malignancies [32,150-152], but there is a lack of evidence for this. Little is known about the health gain from a gluten-free diet for screening-detected cases. In our adult population we defined a sub-group of screening-detected

cases, and they experienced symptom relief after initiated treatment for the disease [Paper I]. However, our cases were almost only from risk groups. Both our child study [Paper III], and a study from the United States [220], have shown similar health at the time of screening for those with unrecognized celiac disease and "healthy" persons, which results in doubt concerning the short-term health benefits from having a diagnosis through a mass screening. Studies have indicated that the mortality risk is higher in undetected celiac disease than in the general population but with current knowledge it cannot be determined if a diagnosis increases life length [129-132,206]. To summarize, little is known about the future health benefits from getting a diagnosis in a mass screening and this needs further exploration. [Principle 7]

There are serological markers that help detect celiac disease, with both a high sensitivity and specificity to screen for the disease [28], and there is an accepted classification of small intestinal enteropathy [17]. There are national and international guidelines to help clinicians in deciding who to treat [18,22,197]. Thus, suitable tests and facilities for diagnosis are available, and there is an agreed-upon policy on who to treat. [Principles 3, 5 and 8]

An efficient treatment is available for celiac disease, the gluten-free diet. Adherence to the diet is sometimes difficult [226], and both a relatively high [136,190,221,227], and a relatively low [228,229], adherence have been reported in screening-detected groups, indicating that good treatment is possible in certain settings. Acceptance of a gluten-free diet can be questioned, especially in symptom-free cases. In the UK about one fourth of clinically diagnosed cases without classical symptoms regretted getting their diagnosis [230]. Following a gluten-free diet might even cause nutrional problems that would have been avoided on a gluten-containing diet [231], and the diet is also more expensive [167,203]. Nevertheless, acceptance of the treatment is likely to be high enough for a potential mass screening. [Principle 2, and the part about facilities in principle 3]

Acceptability of a celiac disease mass screening process has only been investigated in the ETICS study [46]. Children were asked how they felt about the screening process after blood sampling was done. The conclusion was that they managed to cope well and gain confidence, despite some anxiety [232]. Further, parents' WTP for a screening of their child gave some support for the procedure [Paper IV], as did a follow-up of screening-detected children one year after diagnosis [233]. Only 6% refused a small intestinal biopsy, indicating that most, but not all, accepted the screening process [19,233]. [Principle 6]

Two health economic evaluations have investigated the cost-effectiveness of a celiac disease mass screening [194,195]. Neither was able to respond fully to the cost-effectiveness issue, although they indicated that a mass screening is cost-effective based on certain assumptions. My colleagues and I therefore plan to conduct a more comprehensive health economic evaluation in the near future. New information from this thesis about health care

consumption and missed working days [Paper I], HRQoL for children and adults [Paper II & Paper III], and parents' WTP for a celiac disease mass screening of their child [Paper IV] will be included in the evaluation. [Principle 9]

Wilson and Jungner's last principle states that "case-finding should be a continuous process". This condition is not really relevant with respect to a celiac disease mass screening. However, an important issue is whether a celiac disease mass screening should be repeated [165], and as celiac disease can occur at any time in life, this might be justified. [Principle 10]

Concluding remarks

In this thesis it was shown that adults with untreated celiac disease experience poor health. It was also shown that many today still have to live with this burden for a long time, although there are signs of a decrease in the delay to a celiac disease diagnosis over time. Importantly, diagnosis and initiated treatment reduced this burden, as clinically detected cases reported both a HRQoL similar to that of the general population and symptom relief. However, it is unclear if the gluten-free diet also has a positive effect in reducing the risk for associated immune-mediated diseases. Children with celiac disease, both clinically-detected and treated and screening-detected, also reported a HRQoL that was similar to that of others. Regarding screening-detected children, who rated their HRQoL before they were aware of their disease, we are still not sure if their health is similar to that of others due to the study design and the instrument used for HRQoL (EQ-5D).

The thesis also covered some of the economic factors for both those with clinically detected celiac disease and for a celiac disease mass screening. Adults with clinically detected celiac disease reported reduced health care consumption and fewer working days missed, and thereby probably increased productivity, after initiated treatment for the disease. Thus, for these factors a diagnosis is likely to lead to savings for both the individual and society. Also, parents on average reported a WTP that was higher than our estimated cost for a celiac disease mass screening of 12-year-olds in Sweden.

This thesis adds information for the mass screening topic. In my opinion there are still too many unresolved issues before a mass screening can or cannot be recommended for celiac disease. Issues needing more research mainly include the natural history of the disease, the potential future health gains for screening-detected cases, and the cost-effectiveness of a mass screening. Further exploration regarding acceptance of the screening procedure and the treatment is also important. If a mass screening is recommended, it is likely that it will be for certain populations based on information such as the prevalence of celiac disease, acceptance of the screening procedure, and acceptance of the treatment.

This thesis indicates some research areas within the celiac disease field that I think should receive priority. Among these are: i) methods to reduce the delay in celiac disease diagnosis, with focus on awareness of celiac disease among physicians, ii) the cost-effectiveness of a mass screening, based on a more complete health economic evaluation than previously carried out, iii) the natural history, health benefits and consequences for celiac disease patients detected through a mass screening.

The researcher

I received my Master's Degree in Mathematical Statistics in 1997, and was shortly thereafter accepted as a PhD student in Mathematical Statistics at the Swedish University of Agricultural Sciences. I knew very little about what it would mean to be a "researcher", but it seemed like an opportunity to increase my knowledge and skills. I completed my Licentiate Degree in 2003 with focus mainly on forestry, remote sensing, image analysis, spatial statistics, and classification methods. The "field work" comprised computer simulations based on already existing data, i.e. very different from field work within the medical field. Thereafter, I was employed for 18 months as biostatistician at the pharmaceutical company AstraZeneca, where I had my first contact with the medical field. It was a valuable experience that has been of benefit in my current work.

After finalizing my licentiate thesis I did not think I would be involved in research again at the university level; nevertheless, in less than two years I was back again. I wrote in the acknowledgments section of my licentiate thesis: "It is certainly worth the effort to go through the time as a PhD student but I guess that it is something that you have to do only once in your life". I could not imagine starting on a new PhD thesis, but I definitely have no regrets about the fact that I did so! It is worth mentioning that I applied for my current position solely for the opportunity to do research again, and a PhD thesis was then highly prioritized.

In 2005 I was given the opportunity to join the celiac disease research group that my supervisor Anneli Ivarsson (pediatrician and epidemiologist) was forming. At that time I knew very little about celiac disease. During my first two years I was mainly involved in working with the ETICS study, where I was responsible for different parts, including the data handling. I took some courses, but my own research did not start until I was accepted as a research student in the summer of 2007. I was well prepared for what was involved in doing research, but there was still a huge difference between doing research in the mathematical statistics field and the medical field.

I am grateful for having had the opportunity to do research within the celiac disease field, and I think that my extensive involvement in a large study (ETICS), and also a small-scaled study (the questionnaire study on Swedish adults with celiac disease), will be of great importance regarding my future career path. My plan is to continue with research within the celiac disease field, but also to do research within other fields, and to take advantage of my unique combination of skills in health economics, epidemiology and statistics. I have ideas concerning research questions where I think my skills will be beneficial, and hopefully I will be able to implement some of these ideas in the near future.

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