Mass Screening for Celiac Disease
A Public Health Intervention from the Participant Perspective

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Thanks for sharing the journey!
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Abstract

**Background**  Celiac disease (CD) is a chronic disorder in genetically predisposed individuals in which damage to the small intestine is caused by eating foods containing gluten. The prevalence has been shown to vary from around 1-3%, but most people with CD are undiagnosed. An option for finding those with unrecognized CD would include screening the general population, i.e., mass screening. However, screening identifies a pre-disease or disease condition in people who are presumed healthy and have not sought help. Therefore, the impacts of the screening process and being diagnosed through screening should be explored before such a public health intervention is considered. A population-based CD screening study involving 12-year-olds was undertaken in Sweden and provided an opportunity to explore these issues related to CD screening.

**Aims**  To make inferences about the potential impacts mass screening for CD can have on participants by exploring experiences and outcomes for participants involved in CD screening study.

**Methods and Subjects**  Both qualitative (short written narratives) and quantitative (questionnaires with EQ-5D instrument) methods were used. Children who participated in the CD screening study were invited to write narratives at the time of the screening, before screening results were known, describing their experience with the screening (n=240). The EQ-5D instrument was used to measure and compare health-related quality of life reported by participants at the time of the screening and one year after the screening-detected participants received their diagnosis (screening-detected n=103, referents n=483). Those with screening-detected CD were also invited to write narratives one and five years after their diagnosis. In these narratives the adolescents described how it felt to be diagnosed with CD, how it felt to live with CD, and if they thought all children should be screened (one-year follow-up n=91, five-year follow-up n=72).

**Results**  Even though some children experienced fear and anxiety during the screening, overall they had, or were provided with, tools that allowed them to cope well with the screening. The health-related quality of life reported by those with screening-detected CD was similar before and one year after diagnosis (and similar to that of the referents). We also found that after five years of living with the diagnosis there had been maintenance and evolution in the beliefs and practices of these adolescents. Being detected through screening and the threat of complications impacted how they felt about the diagnosis, coped with the gluten-free diet, and what they thought about CD screening. Five years after the screening-detected diagnosis the adolescents have adjusted to
the disease and adapted new habits and coping strategies to deal with the gluten-free diet. However, there are still those who doubt the accuracy and benefit of the diagnosis.

**Conclusions** Our findings suggest that it is possible for participants to avoid excess anxiety during CD screening. However, there was not consensus among participants that being detected and treated had improved their health-related quality of life or that the immediate benefits outweighed the harm caused by being detected in this way. When considering mass screening, the affect on the participants is important to take into account and our findings shed light on some of the potential impacts a CD mass screening could have on participants.
Original Papers

This thesis is based on studies with corresponding original papers that will be referred to throughout as Papers I-IV


IV. Nordyke K, Rosén A, Emmelin M, Ivarsson A. Internalizing the threat of risk - A qualitative study about adolescents’ experiences living with screening-detected celiac disease 5 years after diagnosis (Submitted).

Papers I and II are reprinted courtesy of SAGE publishing
Paper III is reprinted courtesy of BioMedCentral
# List of Abbreviations

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<tr>
<td>CD</td>
<td>Celiac Disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>ETICS</td>
<td>Exploring The Iceberg of Celiacs in Sweden</td>
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<tr>
<td>EQ-5D</td>
<td>Euroqol-5 Dimension Instrument</td>
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<tr>
<td>GFD</td>
<td>Gluten-Free Diet</td>
</tr>
<tr>
<td>GI</td>
<td>Gluten Intolerance</td>
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<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<td>QALYs</td>
<td>Quality-Adjusted Life Years</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

The potential for celiac disease (CD) mass screening to be implemented as a public health intervention is debated (1-2). However, the impacts of such a screening are not fully understood. In this thesis, I highlight the perspectives from participants who took part in a population-based CD screening and in light of screening history and theory make inferences regarding mass screening for CD as a public health intervention.

Background

Celiac Disease

CD is a chronic disorder in genetically predisposed individuals in which small intestinal immune-mediated enteropathy is precipitated by dietary gluten (in wheat, rye, and barley) (3). Most individuals develop oral tolerance towards gluten; however, in some genetically susceptible individuals ingestion of gluten proteins triggers an immune response that results in chronic enteropathy (4-5). The prevalence is generally reported to be about 1%, but an increase in occurrence over time has recently been reported in several countries, including Sweden (6-13). In Sweden, an epidemic of CD in children below two years of age demonstrated that CD is not only related to genetic predisposition and gluten, but also to environmental factors (6, 14-17).

The onset may occur at any age and the development of CD involves complex mechanisms of interaction between genetic, immunological, and environmental factors (18-23). Because of the shared genetic markers, individuals who have first-degree relatives with CD or have other autoimmune diseases (e.g. diabetes mellitus, autoimmune thyroid disease, juvenile chronic arthritis) have an increased risk of also having CD (4, 24-27). Contributing environmental factors are not completely understood (16, 28-35), but there is evidence that infant feeding practices influence CD risk all the way up to 12 years of age (6).

Health Consequences

The health consequences of untreated CD can be related to malabsorption resulting from the intestinal enteropathy, or systemic related to the body’s immunologic response (4, 20, 36). Failure to thrive, abdominal discomfort, diarrhea, and irritability have been considered typical symptoms, but consequences may also include decreased quality of life, delayed puberty, anemia, depression, and low bone mineral density (1, 8, 20, 37-39). The broad spectrum of symptoms can vary between individuals and within an individual over time (1, 3, 40-43).
It is unclear if untreated CD is associated with increased mortality, but mortality does seem to be associated with the severity of the mucosal lesion and the quantity of gluten consumed before and after diagnosis (44-49).

**Treatment**

A strict, lifelong adherence to a gluten-free diet (GFD) is the current treatment for CD. In most patients the enteropathy and symptoms will resolve when gluten is excluded from the diet (20, 50). It has been suggested that adhering to the diet may result in inadequate dietary intake of macronutrients, minerals, and vitamins (51). However, the nutrient and energy intake of adolescents diagnosed with CD in childhood has been shown to be similar to that of healthy controls (52). Although physical benefit can be achieved by following the GFD, it also poses challenges. The GFD can be considered costly, complex, and impacts all activities involving food (53). Women have been found to be more likely than men to experience the disease as a burden and to suffer from emotional distress related to the GFD (53-57).

**Diagnosis**

Initial testing involves serologic markers that have a high predictive value in both children and adults (58-61). Diagnosis is based on a biopsy of the small intestine that reveals intestinal enteropathy, however genetic testing is also debated as a step towards diagnosis (62-66). Recent guidelines suggest high values of serological markers, the presence of predisposing genetic markers, and a clinical and serological response to the GFD may be enough for a definitive diagnosis (62, 66). Females are almost twice as likely as males to have CD (6, 14).

**Often Undiagnosed**

The signs and symptoms may be absent, subtle, or not recognized as CD related and therefore not prompt testing within routine clinical practice (2, 40). The delay to diagnosis can be long and has been shown to be from around 9-11 years (67-68). One study with Swedish adults, showed a six year delay between when care was sought for CD related symptoms and a confirmed diagnosis (68).
Celiac Disease Screening

CD occurrence is often described using the metaphor of an iceberg. Those who are diagnosed are “visable” above the waterline and those with unrecognized CD lie below the waterline, undetected. The only way to find most of those with CD who are “under the waterline” is through screening. Screening for CD may find those with unrecognized CD, but it is a public health intervention that is debated (1-2, 11, 26, 69-71).

Currently within routine healthcare, those who have sought care and are suspected of having CD are tested. Those who are recognized as being at a higher risk may also be tested for CD as part of routine healthcare practice (62-63, 65-66).

The demand for and access to screening shape and are shaped by popular opinion. Self-test kits for CD are available to consumers. In Sweden, the marketing of these kits has started over the last few years. Although it is impossible to pinpoint the impetus, this trend can be driven by, and is driving, public demand (72). Issues regarding over-the-counter screening tools involve various actors and motives (73).

When it comes to disease screening the motives of the health care professionals, population, and industry can clash. A public and transparent discussion about motives and consequences should be something that public health practitioners advocate. In order to make inferences about the potential impacts a mass screening for CD could have I present an overview of general screening history and theory and then describe the aims, guiding frameworks, and methods and findings of the research.
What is Screening?

Health initiatives and screening concepts are shaped by medical, cultural, commercial, and political factors and are thus context- and time-specific (74). In order to give a condensed overview of screening, I will use the context of the evolution of screening practices, policy, and philosophy in the United Kingdom and the United States.

Definitions for screening have changed over time and different agencies have adapted and adopted specific definitions. Screening for disease involves actively seeking to identify a disease or pre-disease condition in people who believe they are well in relation to the condition screened for (72).

Wilson and Junger, commissioned by the World Health Organization (WHO) in 1968, published a paper presenting the principles and practice of screening for disease in a simple and clear manner (75). They described various methods for early disease detection that include screening, surveillance, and case-finding approaches (75):

- “Mass” screening: large-scale screening of whole population groups (without selection)
- “Selective” screening: screening of certain high-risk groups in the population; it can be large-scale and considered as a form of population screening
- ”Multiphasic” screening: administering two or more screening tests at the same time in population groups
- ”Surveillance”: long-term process of observation where screening examinations are repeated at intervals of time
- ”Case-finding”: detecting disease and bringing patients to treatment
- “Population” or “Epidemiological” surveys: do not aim to deliver treatment to undetected patients, but instead to study variables of interest
Despite efforts to clarify what screening is, confusion remains as to what constitutes a screening and how to define a “screening-detected case” (72). Screening has been thought of as a medical investigation that is not initiated by the individual who is looking for healthcare; however, screening examinations can also be instigated by individuals (72). People may request screening exams because they are negatively affected by signs or symptoms of a disease, but also because they have been exposed to information about the risk and the specific screening exams that exist (72).

In addition, medical practice standards have evolved to include opportunistic health promotion as part of standard consultations (76). Doctors and other healthcare providers are expected to discuss disease prevention, and that may include recommending and offering screening examinations (76). It has even been suggested that screening and behavioral counseling could be routinely done pediatric primary care providers (77).

Purposes of screening include: to reduce the risk of future ill health, to give information (even if the risk cannot be changed), to promote individual autonomy, research, and to benefit society (if resource expense and loss can be averted) (72-73, 78-79).

Evolution of Screening

The early screening movement was aimed at preventing future disease, collecting scientific material for pathology and disease exploration over time, influencing patient choice and access, and minimizing risks for government, insurance companies, private corporations (72, 78, 80).

Periodic Health Examinations

Within the medical community, Dr. Horace Dobell (physician in United Kingdom) gave a series of lectures in 1861 encouraging physicians to perform periodic health examinations on individuals who were considered well (72). He encouraged practitioners to focus on the prevention of future disease, especially in relation to living conditions, co-existing disease, and causes of disease. At a meeting of the American Medical Association in 1900, Dr. George Gould presented a paper in which he recommended annual health checks of patients to collect data on individuals from birth to death (72).

The medical community remained engaged in the issue and in 1922 the American Medical Association officially endorsed the practice of periodic health examinations. These periodic exams would allow for illnesses that were unrecognized to be caught and treated, they would provide data that would increase the understanding of what causes diseases and how
to prevent them, and they would provide vital statistics (72, 80). There was also motivation to protect professional interests, as public health programs with government delivery and control threatened exclusive access to patients (72).

Governments used periodic checks on potential war recruits and later aimed at improving living conditions and child health (74, 78, 80). Insurance companies used medical exams as a way to classify and track policy holders (72). Employers adopted periodic exams to enhance the health of their workers and as a way to protect themselves against injury compensation claims by having access to information suggesting causal pre-existing conditions (72).

By the 1950’s periodic health examinations were a standard practice in the United States. They were thought to reduce healthcare utilization and costs as well as being a way to control chronic disease (78).

**Screening Critique and Recommendations**

In the 1940’s and 1950’s there were screening programs that were successful in reducing cases of tuberculosis and syphilis (although these campaigns were discontinued once the prevalence fell) (78). However, some screening programs also beginning to elicit critique (72, 80). Questions regarding the evidence for programs and the procedures used prompted discussion and research aimed at developing specific guidelines and recommendations for a more standardized approach to screening (81). The Kaiser Permanente study (1964) and the South East London study (1967) were trials that were carried out to evaluate multiphasic screenings using a case control approach. Results from both showed no significant benefit from the periodic screening exams (82-83).

There was also increasing concern about the claims and recommendations for screening that were being made by authorities based on no particular evidence (72). Therefore, the Nuffield Trust, under the leadership of Tom McKeown a Professor of Social Medicine in the United Kingdom, assessed 10 existing or proposed screening activities. The 10 screening activities were: bacteriuria in pregnancy, breast cancer, cervical cancer, deafness in childhood, diabetes mellitus, glaucoma, iron deficiency anemia, phenylketonuria, pulmonary tuberculosis, and rhesus hemolytic disease of the newborn. They found that six of these programs were seriously deficient and that even for the four that had valid evidence (deafness in childhood, pulmonary tuberculosis, rhesus hemolytic anemia, and phenylketonuria) comprehensive information was still lacking (72).
It was during the 1960’s that Dr. Wilson from the United Kingdom was sent to North America by the WHO to review and report on the active screening situation underway there (78). Wilson, along with a clinical chemist, Gunnar Junger published the WHO monograph that discussed screening principles and practice (75). They described 10 criteria for case finding that should be met before screening is even considered as an option (Table 1). These criteria are still used as the gold standard when discussing screening requirements (73, 75).

**Table 1. Wilson and Junger criteria (75)**

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<tbody>
<tr>
<td>1</td>
<td>The condition sought should be an important health problem</td>
</tr>
<tr>
<td>2</td>
<td>There should be an accepted treatment for patients with recognized disease</td>
</tr>
<tr>
<td>3</td>
<td>Facilities for diagnosis and treatment should be available</td>
</tr>
<tr>
<td>4</td>
<td>There should be a recognized latent or early symptomatic phase</td>
</tr>
<tr>
<td>5</td>
<td>There should be a suitable test or examination</td>
</tr>
<tr>
<td>6</td>
<td>The test should be acceptable to the population</td>
</tr>
<tr>
<td>7</td>
<td>The natural history of the condition, including development from latent to declared disease, should be adequately understood</td>
</tr>
<tr>
<td>8</td>
<td>There should be an agreed policy on whom to treat as patients</td>
</tr>
<tr>
<td>9</td>
<td>The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole</td>
</tr>
<tr>
<td>10</td>
<td>Case-finding should be a continuing process not “a once and for all project”</td>
</tr>
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Current Screening Philosophy

Screening philosophy has evolved over time. Early beliefs were founded on confidence in the power of science, technology, and medicine. Then such confidence was challenged and efforts were taken to move towards a practice and policy founded on rationalism, evidence, organization, economic evaluation, and an ethical duty to be certain that good exceeded harm (72, 84).

Genetic science is also adding to the landscape of screening discussion and practice (73-74). Genetic counseling is recommended pre- and post-testing and to be a process of communication that enables the patient to cope with possible psychological and social consequences (73).

In addition, screening philosophy may be forced to reckon with: declining medical, scientific, and expert authority, increased expectations for elimination of risk and complete and balanced information, growing availability of tests, transition away from centralized state-organized provision of care and services, and tensions concerning the funding of healthcare (72).
Screening as a System

With the goal being to understand screening and improve outcomes for the population, we should think in terms of screening systems, not just screening tests (72). Instead of viewing screening as offering and administering a test, it should be thought of as a service that encompasses the entire process that leads to the control of disease, including the diagnosis and treatment (85). Below is a figure that has been suggested by Raffle and Muir as a way to visualize screening as a system (72) (Figure 1).

![Figure 1. Raffle & Gray's screening diagram: map of core and support activities *Adapted from Raffle & Gray (72)*](image)

Ethics of Screening

Screening is ethically different from clinical practice. When a patient seeks out advice for a complaint, the ethical duty of the physician is to do the best that is possible for the patient with the knowledge and resources available (85). With screening, those who participate are not patients and most of them will not become patients. They should not be expected to submit to the inconvenience or anxiety caused by the investigation without the prospect of benefit for them or the community (85).
There is no single set of ethical principles to guide judgments about screening policy, but principles of individual and patient rights, equity, and the greatest good for the greatest number can be of assistance (72, 85-86).

Those who are involved in public health have a responsibility to consider the ethical implications of screening policy and programs (84). This includes researchers within the field, policy makers, and those who are in a position to review and critique proposed and ongoing screening programs.

Screening from Different Perspectives

Individuals assume that the risk of side effects mostly applies to others. They are exposed to information about available screening exams that may exaggerate benefits of diagnosis and not explicitly or accurately report on potential harms. It is a common phenomenon that someone who has a screening-detected abnormality feels thankful for the screening program, but this is not enough to justify screening (72). Many people want the reassurance of a negative test. This “reassurance illusion” means that those deemed normal feel good, even though their risk has not really changed (72). This may lead to future symptoms being ignored, a belief that diagnostic tests are more reliable than they are, dependence on regular medical tests, and resources being diverted away from caring for the ill (72). In addition, when a disease is diagnosed it becomes more visible and this leads to the “popularity paradox”. This means that the more a disease is diagnosed by screening, the more popular the screening becomes as participants believe they have been lucky to be detected (72).

From a healthcare perspective, treatment means there is the chance of benefit for the individual. It is also assumed and accepted that for the individual there is the possibility the treatment includes a risk of side effects (73, 87).

The public health perspective considers the benefit and harm of screening to the individual and the population, and this is contrary to the belief that screening is every individual’s right (72-73). Public health practitioners should engage in producing and disseminating evidence about the impacts of screening so that public opinion can be shaped by balanced information.
Benefits and Harms

The benefits from screening should outweigh the disadvantages to make screening worthwhile from a public health perspective (79). The magnitude of harm and benefit both for the individual and population should be considered (Table 2).

Table 2. Chamberlain’s screening benefits and disadvantages (79)

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Improved prognosis for those detected</td>
<td>Longer morbidity for those detected whose prognosis remains unaltered</td>
</tr>
<tr>
<td>Less radical treatment which cures some early cases</td>
<td>Overtreatment of questionable abnormalities</td>
</tr>
<tr>
<td>Reassurance for those with negative test results</td>
<td>False reassurance for those with false negative results and anxiety and sometimes morbidity for those with false positive results</td>
</tr>
<tr>
<td>Resource savings</td>
<td>Resource costs</td>
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</tbody>
</table>

Some individuals may have a disease but never develop problems and even if they are detected their outcome remains unaltered by early detection (72). Others may not improve, even when found through screening.

The potential risks associated with the screening tests should be understood and explained to the participants. Measures of diagnostic test performance include sensitivity and specificity. High sensitivity in a tool means catching as many of the cases as possible. It also means there are more false positives, but fewer undetected cases (72). High specificity means fewer false positives but more undetected cases (72). Those with false negative results are given false reassurance the consequences for those given false positives should also be considered.

In addition, in order to justify screening the resources saved must justify the resources spent and be and weighed against those of alternative strategies (85).
Screening Evaluation

Interpreting and evaluating screening evidence involves considering the dynamics of the entire screening system and can lead to a better understanding of the outcomes (72, 88). There are criteria for evaluating screening systems, however evaluating the entire CD screening is not the aim of this thesis. In this thesis it is the participant experience and outcomes, situated in different stages in the screening system, that are the focus.

Evaluating Celiac Disease Mass Screening

Considering what is known about CD and the potential impacts mass screening for it would have is necessary to guide policy if such a public health intervention is to be considered for the future. Some issues regarding CD mass screening remain unclear and knowledge regarding the potential impact on participants is limited.

In order to show what this thesis contributes to the evaluation of CD mass screening, the screening criteria that have been introduced (Tables 1 and 2) are presented in relation to what is known about CD and CD screening and to the gaps in knowledge that are addressed in this thesis (Tables 3a and 3b).

Table 3a. Evaluating celiac disease mass screening within the context of recommended criteria

<table>
<thead>
<tr>
<th>Chamberlain's Screening Benefits and Disadvantages</th>
<th>CD mass screening</th>
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<tr>
<td>Improved prognosis for those detected</td>
<td>The morbidity and mortality for those who are screening-detected are unclear</td>
</tr>
<tr>
<td>Longer morbidity for those detected whose prognosis remains unaltered</td>
<td>The benefit of the GFD for those who are screening-detected is not completely clear</td>
</tr>
<tr>
<td>Less radical treatment which cures some early cases</td>
<td>There will be those with negative markers who later develop CD and also those who will have unnecessary biopsies</td>
</tr>
<tr>
<td>Overtreatment of questionable abnormalities</td>
<td>The onset can occur at any age so repeated screenings and follow-ups of borderline cases may be necessary</td>
</tr>
<tr>
<td>Reassurance for those with negative test results</td>
<td>Diagnostic tools are relatively reliable and safe, but not without risk</td>
</tr>
<tr>
<td>False reassurance for those with false negative results and anxiety and sometimes morbidity for those with false positive results</td>
<td>The resources of applying a large-scale screening are debated</td>
</tr>
<tr>
<td>Hazard of screening test</td>
<td>Resource savings</td>
</tr>
<tr>
<td>Resource costs</td>
<td>Resource costs</td>
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</tbody>
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Chamberlain’s screening benefits and disadvantages (79) *Issues evaluated in the thesis in bold
Table 3b. Evaluating celiac disease mass screening within the context of recommended criteria

<table>
<thead>
<tr>
<th>Wilson and Junger's criteria</th>
<th>CD mass screening</th>
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<tbody>
<tr>
<td>The condition sought should be an important health problem</td>
<td>CD is fairly common and the majority are undiagnosed, however additional research on the long-term morbidity of untreated CD are needed</td>
</tr>
<tr>
<td>There should be an accepted treatment for patients with recognized disease</td>
<td>Compliance with the GFD can usually offer relief from symptoms and return the intestinal mucosa to a healthy state</td>
</tr>
<tr>
<td></td>
<td>If treatment at an early stage is more beneficial than at a later stage is not known and the impact of diagnosis and treatment on participants who are screening-detected is unclear</td>
</tr>
<tr>
<td>Facilities for diagnosis and treatment should be available</td>
<td>Diagnostic tools are reliable and a treatment is known, however the access to these vary globally</td>
</tr>
<tr>
<td>There should be a recognized latent or early symptomatic phase</td>
<td>Serological markers indicative of CD are considered reasonable for detecting unrecognized CD</td>
</tr>
<tr>
<td>There should be a suitable test or examination</td>
<td>Diagnostic tools are reliable and relatively safe</td>
</tr>
<tr>
<td>The test should be acceptable to the population</td>
<td>The economic burden of applying them on a large scale screening are debated</td>
</tr>
<tr>
<td>The natural history of the condition, including development from latent to declared disease, should be adequately understood</td>
<td>Untreated CD that has been detected through routine health care has been shown to be associated with negative health consequences and increased mortality, however the long-term health consequences of unrecognized CD are unclear</td>
</tr>
<tr>
<td>There should be an agreed policy on whom to treat as patients</td>
<td>The diagnosis may be definitive and the treatment may be defined, but the benefit of treating those who have not sought medical attention related to symptoms are unclear</td>
</tr>
<tr>
<td></td>
<td>As the onset can occur any age it is also not evident when screening would be most beneficial</td>
</tr>
<tr>
<td>The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole</td>
<td>The costs and benefits of applying a large-scale screening are controversial and still debated</td>
</tr>
<tr>
<td>Case-finding should be a continuing process and not “a once and for all project”</td>
<td>Such an infrastructure does not exist and would have to be developed and overseen</td>
</tr>
</tbody>
</table>

Wilson and Junger criteria (75) *Issues evaluated in the thesis in bold
Aims

Overall Aim

To reflect on screening history and theory and make inferences about the potential impacts mass screening for CD can have on participants by exploring experiences and outcomes for participants involved in a CD screening study.

Specific Aims

Paper I: To explore how participants experienced being involved in a CD screening

Papers II and III: To determine and compare the health-related quality of life for those with screening-detected CD before and after diagnosis

Paper IV: To explore how perceptions, practices, and beliefs have evolved five years after screening-detected CD diagnosis
Thesis Overview

The experiences and outcomes of those who participated in a CD screening study, situated in different stages in the screening system, are the focus of this thesis and presented below in Figure 2.

Figure 2. Screening system and thesis *Screening flow diagram adapted from Raffle & Gray (72)
<table>
<thead>
<tr>
<th>Method</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>Qualitative</td>
<td>Quantitative</td>
<td>Quantitative</td>
<td>Qualitative</td>
</tr>
<tr>
<td></td>
<td>Explore how participants experienced being involved in a celiac disease screening</td>
<td>Determine participants' health-related quality of life before diagnosis</td>
<td>Compare participants' health-related quality of life before and one year after diagnosis</td>
<td>Explore how perceptions, practices, and beliefs have evolved five years after screening-detected diagnosis</td>
</tr>
<tr>
<td>Material</td>
<td>Based on participants' short written narratives</td>
<td>Based on questionnaire responses to the EQ-5D instrument</td>
<td>Based on questionnaire responses to the EQ-5D instrument</td>
<td>Based on screening-detected adolescents' short written narratives</td>
</tr>
<tr>
<td>Participants</td>
<td>Children who participated in CD screening (n=240)</td>
<td>Screening participants and their parents at the time of screening (screening-detected children n=147-152)</td>
<td>Screening-detected (n=103) and referents (n=483) at time of screening and one year after diagnosis</td>
<td>Screening-detected one year (n=91) and five years (n=72) after diagnosis</td>
</tr>
<tr>
<td>Analysis</td>
<td>Qualitative content analysis</td>
<td>Quantitative descriptive &amp; analytical statistics</td>
<td>Quantitative descriptive &amp; analytical statistics</td>
<td>Qualitative content analysis</td>
</tr>
</tbody>
</table>

Table 4. Summary of papers included in the thesis
Theoretical Frameworks

The way in which research is carried out is influenced by the theoretical position and ontological and epistemological standpoints of the researcher (89). Here I present the theoretical frameworks and standpoints that motivated and influenced the direction of this research.

Qualitative and Quantitative Approaches

The use of both qualitative and quantitative methods is a pragmatic strategy for addressing different types of research questions or issues and contributes positively to the researcher's "toolkit" (89). In this thesis both qualitative and quantitative approaches were used to compliment one another, to focus on different research aims, and to provide breadth and depth in the research.

A qualitative method was included because we were interested in the participants' interpretations of the screening experience. Qualitative research is described as a way to explore things in their natural settings, while attempting to understand phenomena in terms of the meanings that people bring to them (89-90). By asking the participants to write narratives we sought to gain an understanding of their own beliefs, attitudes, and actions as interpreted by them (91).

A quantitative approach was used in order to measure problems in specific dimensions related to health and to generate data that were suitable for comparison across time and between groups. For this we asked participants to complete questionnaires that included the EQ-5D instrument.

Ontological and Epistemological Standpoints

Ontology concerns beliefs about what there is to know about the world (89). It deals with whether or not reality exists independently of human interpretations, whether there is a shared social reality or just multiple context-specific realities, and whether or not behavior is governed by common laws (89-90). The experiences of the screening participants do not exist apart from their understanding. Through collecting and disseminating results based on data generated by the participants, value is given to their lived experiences, interpretations, stories, and valuations of their own health.

Epistemology is concerned with ways of knowing and learning about the social world and focuses on questions such as how can we know about reality and what is the basis of our knowledge (89-90). It concerns the relationship between the researcher and the researched (89-90).
I was interested in the participants’ descriptions of their experiences, but have a preunderstanding that colors how I approached and conducted the research and disseminated the results. Throughout the research process I did not aim to give the impression that I had no history or preunderstanding but instead worked to be open, reflective, and transparent.

**Dialectics**

Dialectics is a way of thinking and imagining the world (92). Thinking about and accepting that the world is made up of processes, relationships, dynamics, conflicts, and contradictions is the foundation of the dialectic theory (92). In accordance with dialectic theory, research should be concerned with how these things are intertwined to provide relevant answers to research problems (92). Within nursing this philosophy is embraced as a way to advance from partial, one-sided knowledge to a more comprehensive understanding necessary for holistic care (93).

These theories and practices have influenced me to focus on the participants’ experiences. Asking the participants for their stories and self-reported health was an attempt to capture a comprehensive and holistic understanding of their experiences.
Concepts

Mass Screening

In this thesis and the studies included in it, I refer to “mass screening”. Mass screening can be defined as large-scale screening of whole population groups (75). The CD screening study that is the basis for the research can be used as a platform to envision a mass screening scenario. The cross-sectional, population-based CD screening study that this thesis is based on is described in detail later.

Other research that claims to be representative of screening-detected individuals is usually based on those who are tested and diagnosed because they have been considered to have an increased risk for CD. The screening study this thesis is rooted in involved 12-year-olds from specific regions in Sweden, but they were not screened prior to the study for risk factors. Consequently, in this thesis the participants who had positive serological markers, followed up with a biopsy confirming a CD diagnosis, are referred to as “screening-detected”. The participants who entered the study with CD already diagnosed through routine healthcare prior to the study are referred to as “previously diagnosed” or “clinically-detected”.

Risk

Screening may be in demand from individuals, populations, health professionals, and/or private industry, but screening introduces risks as well as potential benefit. Anthony Giddens, a social scientist who addressed risk and modernity, uses a descriptive metaphor that I find useful when thinking about screening (94). He describes a giant and massive force - a “juggernaut” - that moves forward, rambling over everything and everyone in its path. People steer the juggernaut, but can not totally control it, and there is always the threat of losing control of it. For those who control it the juggernaut can bring rewards, but it can also bring dangers, including constant anxiety that control could be lost at any moment, threatening the lives of many. Because of this and the feeling that the juggernaut is far removed in terms of space and time, people are forced to develop a sense of trust in the juggernauts and those who control them.

This metaphor can be applied to screening systems. Risks can be caused by mistakes made by those who design and run the screening system, because of unforeseen or unintended consequences, or because new knowledge that is generated that may change the nature and consequences of the screening (94).
Health-Related Quality of Life

Health-related quality of life (HRQoL) and quality of life (QoL) are concepts that refer to the physical, psychological, and social domains of health as distinct areas influenced by a person’s experiences, beliefs, expectations, and perceptions (95). HRQoL is often measured and used to evaluate healthcare interventions, to understand the burden of disease, and to prioritize allocation of resources (96). HRQoL and QoL are measured with generic- or disease-specific quantitative instruments (95).

Chronic diseases and their treatments impact HRQoL (86, 97-98). Expectations, experiences, and coping abilities affect perception of health and individuals with the same diagnosis and physical “health” may experience different HRQoL (86, 95-96).

Research addressing HRQoL and QoL in people with CD is almost always based on those who are clinically-detected or selected for screening because they are considered at high risk (43, 68, 99-115) and is typically focused on adults (43, 68, 99, 102-113, 116). Some studies have explored the HRQoL of children and adolescents with CD. In a sample of children and adolescents from a Dutch CD society, the QoL in those who were clinically-detected and treated was similar to that of the healthy referent sample, although adolescent girls with CD reported more physical complaints than the adolescent boys with CD (114). In a case-control study, German and Austrian adolescents retrospectively reported on QoL (115). The adolescents who were diagnosed with CD and initiated treatment early (before 6 years of age) were compared to those diagnosed late (after 6 years of age). It was found that those with a late CD diagnosis reported poorer QoL in the areas of school, physical health, and CD associated burden compared to those who received an early CD diagnosis (115).

The HRQoL of screening-detected individuals could differ from that of clinically-detected or high risk patients, but exactly how is still unclear. In this thesis the concept of HRQoL is used to address whether the participants experienced benefit from being diagnosed as a result of the screening.
Study Context

Celiac Disease Screening Study in Sweden: ETICS - Exploring The Iceberg of Celiacs in Sweden

Sweden experienced an epidemic of CD in children under 2 years of age (1984-1996) resulting in a unique opportunity to increase knowledge about the causes and consequences of the disease (14-15, 17, 117).

It was found that during the epidemic there was an increase in the proportion of infants introduced abruptly to large amounts of gluten without ongoing breastfeeding and that a more favorable practice was to introduce gluten in small amounts while the infant was still being breastfed (15, 17).

A two-phased study, known as ETICS - Exploring The Iceberg of Celiacs in Sweden was undertaken during 2005/2006 and 2009/2010 to further investigate cohorts of children (born 1993 and 1997) with different infant feeding practices (6). ETICS included five regions in Sweden (Figure 3).

Figure 3. The five Swedish regions involved in a celiac disease screening study known as ETICS – Exploring the Iceberg of Celiacs in Sweden
Recruitment/Participants

Children from both the birth cohorts were invited to participate when they were 12 years of age (sixth grade). Invitation letters requesting parental consent were sent to their homes (Appendix 1). The letters included information about CD, how it is diagnosed and treated, and specifics about the screening study. The letter also addressed advantages and disadvantages of participating, the confidentiality policy, contact information for the responsible doctor at each site, and included the study’s website address.

From the 1993 child cohort, 10,041 were invited, 7,567 (75%) agreed to participate, and 7,208 (72%) had CD serological markers analyzed (118). From the 1997 child cohort, 8,284 were invited, 5,712 (69%) agreed to participate, and 5,424 (65%) had CD serological markers analyzed (6). The proportion of girls and boys who participated was similar in both cohorts (48% girls in 1993 and 49% girls in 1997) (6).

Screening

The screening took place in the children’s schools where blood samples were collected by research nurses in cooperation with the school nurses. This environment is a logical setting, as some child health services in Sweden, such as vaccinations and periodic health exams, take place in the schools with school nurses and doctors.

Diagnosing and Intervening

After the blood samples were analyzed, those suspected of having CD were referred to their local pediatric department for an intestinal biopsy to confirm or dismiss the diagnosis (118). Upon diagnosis, a clinical referral was made and the GFD was recommended. As part of the screening study, qualitative and quantitative data were also collected from the participants and their parents during the study and at follow-up one and five years after diagnosis.

ETICS Screening Results

From the 1993 cohort 151 (2.1%) screening-detected and biopsy-confirmed CD cases were detected (80 girls, 71 boys) (6). Combined with the clinically-detected cases (n=66, 0.87%) the total prevalence of CD in this cohort was 2.9% (n=217) (6). From the 1997 cohort 89 (1.6%) screening-detected and biopsy-confirmed CD cases were detected (57 girls, 32 boys) (6). Combined with the clinically-detected cases (n=34, 0.60%) the total prevalence of CD in this cohort was 2.2% (n=123) (6).
The prevalence ratio between these two cohorts was 0.75 (95% CI: 0.60-0.93) (6). This statistically significant difference suggests that infant feeding influences CD risk all the way up to 12 years of age and supports a practice of introducing gluten into the infant’s diet gradually, in small amounts, and preferably while still breastfeeding (15, 119-121).

For both cohorts the screening-detected cases accounted for 2/3 of the children with CD and the clinically-detected cases accounted for 1/3 of the total with CD. Indeed, the majority of those with CD were only found at this time because of the screening.

**Ethical Considerations**

The ETICS study was approved by the Regional Ethical Review Board of Umeå University [drb 04-156M], and the Swedish Data Inspection Board. Informed consent was obtained from the legal guardian/s of the participating children. In an effort to promote the autonomy of the children there was also information in the invitation that was specifically addressed to the child. In order to use terminology the population would be familiar with the term “gluten intolerance” was sometimes used in the invitations and questionnaires. The children could decide to withdraw from the studies anytime during the screening process and follow-up studies.
Opportunity for Celiac Disease Screening Evaluation

ETICS was planned not only to determine and compare CD prevalence in the two birth cohorts, but also to advance knowledge about CD and screening for CD. Studies were planned, or designed along the way, to evaluate many of the dynamic and complex issues related to CD and CD screening (Figure 4).

![Figure 4](ime.png)

**Figure 4.** ETICS studies addressed issues related to celiac disease and celiac disease screening
Material and Methods

This thesis is based on the first phase (2005/2006) of the ETICS study and one- and five-year follow-up studies. Qualitative and quantitative approaches were used. Qualitative data (short written narratives) was used to explore the participants’ experience with the screening and after diagnosis. Quantitative data (questionnaires including the EQ-5D instrument) was used to measure and compare HRQoL before and after screening-detected diagnosis.

Data Sources

Short Written Narratives (Papers I and IV)

Papers I and IV are qualitative studies based on the participants’ short written narratives. The narratives were elicited from the participants with experience in the phenomena we were interested in, i.e., taking part in a CD screening and being diagnosed through a CD screening.

Written narratives are generated data that involve reconstruction, reprocessing, and retelling of experiences (89). They provide insight into peoples’ perspectives, interpretations, and meanings that they attach to experiences (89). Narratives are often described as “stories” about events that people organize and relay to convey meaning (90-91). This kind of storytelling may be a form of expression that helps people make sense of events. Narratives are created for specific audiences at specific times and can be captured as written, spoken, and visual material (91). Narrative theory initially developed from examining literary works; however, narratives have always been a part of the human experience and are present in myths, paintings, conversations, diaries, health records, photographs, etc. (91) All text and talk are not narratives. To have meaningful patterns a narrative must have a consequential linking of ideas or events and thus have contingent sequences (91). The subjective nature of narratives, that they involve perspectives rooted in time, place, and personal experiences, is what makes them valuable in understanding the reality of the storyteller (91).

For the study described in Paper I, a pilot study was done with one class to test the instructions and determine if the narratives would capture a variety of experiences and yield enough data. After discussing the pilot narratives within the research group, the instructions were finalized and number and type of classes and children to invite was determined.
In the study described in Paper I, the children were allowed to write in their school classrooms. Their teachers gave them the instructions, the paper on which to write, and envelopes in which to seal their narratives. The narrative writing was guided by written instructions. The instructions conveyed that we appreciated their participation and that we wanted them to write about their experiences. Instructions encouraged them to write in whatever manner suited them, but to address some points. In the instructions used for this study (Appendix 2), the participants were asked to describe:

How it went and how they felt when deciding to participate

How it went and how they felt on the day of the blood sampling

How they felt when waiting for the blood sampling result and

What they think is important to consider for participating children in the future

In the follow-up study described in Paper IV, screening-detected participants wrote short narratives one and five years after diagnosis. For the one-year follow-up participants received the materials mailed to their homes. For the five-year follow-up the doctor at the local pediatric site gave the materials to the adolescents at their clinical visit and they were asked to return the completed narrative to the doctor. Instructions were similar (Appendix 3), but this time they were asked to address:

How it felt to find out they had gluten intolerance

If life became different after they found out

How they thought it worked with food at home and at school and

If they thought it would be good to test all children for gluten intolerance, and if so at what age
In both of the studies, the narratives ranged from a few lines to a few pages and the sequence of the stories usually followed the issues they were asked to address. I transcribed the narratives from the screening phase and the five-year follow-up. The one-year follow-up narratives were transcribed by a research assistant. The narratives were transcribed verbatim and slang and profanity were included in the transcriptions in order to remain as close to the adolescent’s intended meaning or “voice”. The responses were varied and deep enough from both boys and girls so that variation in experiences was captured.

Self-Reported Health on EQ-5D (Papers II and III)

In order to collect measurable and comparable quantitative data we used questionnaires that were distributed at the time of the screening, before results of the screening were given (Paper II), and questionnaires that were mailed to the participants’ homes one year after diagnosis (Paper III). Both questionnaires included the EQ-5D instrument.

The EQ-5D instrument can be used as a generic HRQoL instrument. Participants can complete it themselves. It asks them to describe “your health today” by reporting the severity of problems in five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression and marking a thermometer-like visual analogue scale (VAS) for health today from worst to best imaginable (0-100) (Appendices 4 and 5).

For the studies described in Papers II and III, we collaborated with Swedish representatives from the Euroqol group (www.euroqol.org) and negotiated in order to use the “Swedish child-friendly pilot version of the EQ-5D instrument” (Appendix 4). This version was developed by the EuroQol international task force group based on the EQ-5D youth version (Appendix 5) and was adjusted after testing and piloting in Sweden (122-125). It differs slightly from the standardized adult version. The dimensions in the “Swedish child-friendly pilot version” are referred to as: ability to move, looking after myself, doing usual activities, having pain or discomfort, and feeling worried or sad. Also, instead of reporting level of severity as no problems, some problems, or severe problems, the children are given choices that indicate they have difficulties in the dimension. This is because it was discovered during piloting that using the word “problem” triggered inferences to being a “problem child” (122).

For the remaining description and discussion I refer to the “Swedish child-friendly pilot version of the EQ-5D instrument” as EQ-5D and use the standard dimension labels.
The health status reported on each dimension can be converted into scores and the sum of the health scores can be used to calculate “quality-adjusted life years” (QALYs) (126-127). QALY calculations are based on information generated from quality of life indices combined with information about the number of life years gained from an intervention (127). Since at the time there were no QALY reference indices for children based on applied child questionnaires, I did not convert the health status responses to health scores or QALYs. However, I believe our data and findings capture elements related to the physical, psychological, and social domains of health and therefore fit within the definition of HRQoL (95-96).

For this reason the findings from these studies offer valuable insight related to the concept of HRQoL and I refer to it this way in the thesis and papers.

**Participants**

The participants were about 12 years old at the time of the screening (Papers I and II). The participants included in the follow-up studies (Papers III and IV) were about 13 years old at diagnosis and about 15 and 18 years old during the follow-ups. They would also soon be exiting from child education and health services. This period in life includes great physical, cognitive, and developmental changes (98, 128). Based on this, and having met the children during the screening fieldwork, I refer to the participants at the time of the screening as children and during the follow-up periods as adolescents.

**Qualitative Studies (Papers I and IV)**

In Paper I, 240 out of the 271 children invited wrote narratives (107 girls, 109 boys, 24 sex unknown). They wrote after blood sampling, but before they knew the results of the test. They were not differentiated based on whether or not they had CD.

In Paper IV, of the 151 screening-detected adolescents, 91 (49 girls, 42 boys) wrote narratives one year after diagnosis, 72 (39 girls, 33 boys) wrote narratives five years after diagnosis, and 43 wrote both at the one- and the five-year follow-ups. One region did not return any narratives for the five-year follow-up.

**Quantitative Studies (Papers II and III)**

In Paper II we included children with 1) screening-detected CD, 2) previously diagnosed CD, and 3) without CD (“non CD”) who had participated in the screening study.
We also included their parents, who filled out questionnaires mailed to their homes. Questionnaires were received from 7,218 children (3,490 girls and 3,728 boys) and 6,524 parents. The response numbers varied between instruments and dimensions. Of the 7,218 children who returned questionnaires, 98% (n=7,052-7,071 depending on dimension) met inclusion requirements and reported on at least one dimension from the descriptive system and 98% (n=7,051) responded to the VAS.

In Paper III, cases were defined as those with screening-detected CD and referents as those without CD who had participated in the screening study. At the time the cases and referents were being selected, there were 207 children with CD (included screening-detected and previously diagnosed) and four referents per child were randomly chosen with the proportion of girls and boys in the referent group to match that of the cases. Responses were included for the screening-detected cases and referents when they had provided answers on all dimensions and on the VAS at both baseline and follow-up (cases n=103: 56 girls, 47 boys and referents n=483: 275 girls, 208 boys) (Figure 5).

Figure 5. Participants of a celiac disease screening study who reported on health-related quality of life one year after the screening-detected received their diagnosis *Reprinted with permission (Paper III)
Analysis

Qualitative Content Analysis (Papers I and IV)

We chose to analyze the narratives using qualitative content analysis as described by Graneheim and Lundman (129). This method allows for an understanding of subjective interpretations (130). It aims at gaining an understanding of the content close to the text (manifest content) and interpreting the underlying meaning (latent meaning) of the studied phenomena on a more abstract level (129).

The work was a collaborative effort and began by at least two of the authors reading the narratives. In qualitative content analysis an initial step, after having read the whole material, may involve transforming the text into condensed meaning units (129). However, since the texts were concise the coding was done directly from the narratives. To facilitate the coding, the narratives were imported into the OpenCode Program (131).

The codes were discussed between researchers and then clustered into groups on concept maps. This mapping of manifest content into visual clusters with links facilitated moving towards more abstract interpretations. The abstract interpretations were expressed as subcategories and then categories (Paper I) or directly as categories (Paper IV) (Figure 6).

Figure 6. Process of moving from the text, to codes, to category in the qualitative content analysis (Paper IV)
Further interpretation was conceptualized into final themes. In paper I, the theme describes the understanding gained concerning the experience with the screening. In Paper IV, understanding was gained regarding the evolution in perceptions, practices, and beliefs related to screening-detected celiac disease that took place from one year to five years after the screening-detected diagnosis.

**Descriptive and Analytical Statistics (Papers II and III)**

Because QALYs were not calculated, the health status reported for each dimension on the EQ-5D is used as a way of determining and comparing the HRQoL of the participants.

The number and proportion reporting problems were explored for each dimension. Because few reported severe problems, levels of severity were categorized into “no problems” (from level “no problems”) and “problems” (from levels “some problems” and “severe problems”) (126). VAS scores were presented with median values and 25th and 75th percentiles. The statistical software package SPSS 17 (SPSS Inc., Chicago, IL) was used and statistical significance was defined at the 5% level.

In the study described in Paper II, cross tabulations were done separately for each dimension and for baseline and follow-up to illustrate the proportion reporting problems. To test statistical significance of the difference between those who reported no problems and problems within the groups (screening-detected, previously diagnosed, and non CD) the Fisher’s exact test was used as there were few reporting problems. Adjustment for other variables was not done due to the small numbers in the screening-detected and previously diagnosed groups. On the VAS most scored high so we conducted a nonparametric independent samples median test across the groups for child and parent responses. An independent samples Mann-Whitney U test to compare girls’ and boys’ VAS responses. Spearman’s rho test was used to explore the correlation between children’s and parents’ VAS scores.

In the study described in Paper III, cross tabulations were done separately for each dimension and for baseline and follow-up to illustrate the proportion reporting problems. Bivariate logistic regression was used to compare the proportion reporting problems for the cases and referents separately, at baseline and at follow-up, and between the cases and referents at baseline and follow-up, for each dimension. Multivariate logistic regression analyses were also performed for each dimension. In the logistic regression models, case/referent was the dependent variable and problems at baseline and problems at follow-up were independent variables, separately for the bivariate analyses (Crude Odds Ratio) and combined in the same model for the multivariate analyses (Adjusted Odds Ratio).
Sex stratified analyses were done for pain and anxiety dimensions, but not for the other dimensions as there were too few reporting problems to motivate further exploration. The VAS scores of the cases and referents, and the VAS scores for boys and girls within the case and referent groups, were compared using the Mann-Whitney U test. When we compared baseline scores with follow-up scores in the case and referent groups we used the Wilcoxon signed rank test.
Findings

The findings describe the experience of participating in a CD screening study, the HRQoL before and after being diagnosed with CD through screening, and the experience of living with screening-detected CD, all from the perspective of screened participants.

Experience with the Screening (Paper I)

The first study (Paper I) explored how children who agreed to participate in the screening study experienced participating. It describes the experience of the participants after the screening, but before results were known, and aims to clarify if mass screening for CD causes excess anxiety for those being screened.

Our resulting interpretation was that although some children experienced fear or anxiety, they had or were provided with tools that allowed them to cope well.

The children’s stories describe a journey traveled throughout the screening process. The theme, A Journey Towards Confidence, describes the overall experience with the screening. Four categories were developed that describe conditions contributing to the experience and support the overall interpretation: Being Involved, Being a “Good Citizen”, Being Able to Cope, and Being Able to Balance Risk (Figure 7).

**Figure 7.** “A Journey Towards Confidence” – participants’ experience being involved in a celiac disease screening study *Reprinted with permission (Paper I)
Being Involved

This category reflects the importance of involvement in receiving information and deciding to participate. The degree to which the children felt they were involved influenced their overall experience. It seemed that the more the children were involved from the beginning, the more they felt like active participants. The children generally felt that they were information recipients, and they described how they were informed.

“We received a note from school. On the note was a little information about the test and that parents should fill something in if they think their child should be with”

The children also described their role as decision maker when choosing to participate. There were accounts of children deciding themselves or with their parents. Some children stated their parents decided for them, in some cases even when they protested.

“When I took the paper home and showed it to mom and dad they said that I could decide myself if I should do it or not”

“When I gave my mom the notes she immediately said that I should be with but I didn’t want to and began to cry”

Being a “Good Citizen”

Reflected in this category is how the participants felt they had a duty to help. The children were very aware that the screening was part of a study and, although there were a variety of reasons for participating, they described feeling a duty to help and pride in contributing. They wrote that being involved in research is generous and that they were doing it for the greater good.

“When we received the information I didn’t feel at all nervous. I immediately said yes because I knew that it would help research”

The children also trusted they would be treated in a positive way and felt this was a safe contribution. They trusted that they would receive follow-up care. They described beliefs that discovering the disease was important and that receiving a diagnosis was important for treatment.

“It feels fun if the test shows something: to be able to find out if one is allergic to gluten as early as possible so kids don’t have a bunch of problems”
Being Able to Cope

Being able to cope was influenced by the ability to manage sensations and by the support they received. The children described physical and emotional sensations. How they managed these sensations affected how they coped. The physical sensations were often described in relation to the blood test and ranged from barely being felt, hurting, feeling strange, to being horrible. The importance of numbing cream was emphasized, with recommendations that it should always be offered as it minimized pain, helped them feel calm, and gave them confidence. Emotional sensations included feelings of anxiety mixed with confidence. Overall, there were concerns that the blood test would be painful, an uncertainty about what to expect, and feelings of anxiety related to this. Some children stated they were indifferent to the whole process or that previous experiences allowed them to feel secure.

“The day we took the blood test I was very nervous. When they took the blood test I didn’t dare look and it hurt, but it went well”

“The day when I was going to take the blood test I was a little tense but when I took it I hardly felt it. It was much easier than I had thought”

The children gave examples of how they felt supported and what was positive or negative during the screening. Some had discussed the screening with each other or their parents prior to the blood test day. Some described feeling supported by their classmates. Being with a friend was mostly a positive experience, although the presence or actions of peers made the event stressful for some. The children also described interactions with the nurse who drew their blood and gave practical advice about how the nurse could help children cope. Those who coped well may have felt anxious but they had, or were given, tools that helped them manage their anxiety. This led to feeling a sense of accomplishment and increased confidence.

“I think it is important to have a friend with, who can support if one becomes scared or something”

“They should feel calm, because it doesn’t hurt, but most often classmates stir each other up”

“I think they should prepare the kids before the blood test so one isn’t scared when it’s like bam”
Being Able to Balance Risk

This category illustrates that the children were able to balance the risks of screening when they had a realistic understanding of the disease, their vulnerability, and had tamed their anxiety. The children had a realistic awareness of risk, with a general understanding about CD and the risk of having it. Their understanding came from information included in the screening invitation or from knowing someone with the disease. They were concerned about the GFD, but overall they were not alarmed by the screening and often that stated they had not thought much about what the results would be.

“I really hope I don’t have it because my cousin has it and there is a lot she can’t eat”

“When I decided I wanted to be with I wasn’t nervous, only worried that I would have celiac disease. Like, what would happen? Will I be abnormal? It is a relief to get to know if one has it so one doesn’t feel bad later”

“I know almost for certain that I can have flour so I shouldn’t be afraid but I’ll just need to take flour out of my diet”

Anxiety related to feelings of vulnerability varied among the children, but it was not overwhelming. The children described strategies for taming anxiety. They also expressed attitudes of indifference, invulnerability, and anxiety along with confidence that they could cope with the disease.

“I am not nervous for the result because I know that I don’t have any disease”

“Now when I wait for the results I’m a little nervous because one doesn’t want it to be negative” (“negative” here means being told bad news, i.e., they have CD)

Feeling anxious while waiting for the results was rarely described, although some felt anxious after the blood sampling. Balancing risks was not associated only with the risk of possibly having a chronic disease; it was mostly associated with worry related to the blood test, specifically the needle.
Gender Aspects

A pattern was seen in which girls were more likely than boys to express anxiety while making the decision to participate, and to write that it was their parents who had decided they would participate. Both boys and girls described an interest in contributing to research, but this was more emphasized by the boys. Girls were more prone than boys to describe being nervous and to portray the blood test as scary and painful. Girls expressed stronger feelings about the blood test, but it was the boys who were more likely to emphasize feeling nervous while waiting for the results.
Health-Related Quality of Life Before and After Diagnosis (Papers II and III)

The second and third studies measure and compare the self-reported health of the children before and after diagnosis and treatment based on the EQ-5D.

HRQoL at Baseline

For the study described in Paper II, children with screening-detected and clinically-detected CD and children without CD were included. Their parents were also asked to report on their child’s health. Based on the children's responses, no significant differences in the dimensions across the three groups were found (Table 5). There was general agreement between children and parents and most reported no problems in all dimensions.

In the dimensions having pain or discomfort and feeling worried or sad the percentage from each group reporting problems was higher than for the other dimensions (Table 5). We did see the following trends: screening-detected children more often reported problems in the dimensions mobility (4%), doing usual activities (3%), having pain or discomfort (22%), and feeling worried or sad (14%). The exception was in the dimension looking after myself, in which 2% of previously diagnosed children reported problems. In the dimension having pain or discomfort there was a larger gap between groups, as 15% of previously diagnosed children reported problems, while 22% of screening-detected children and 20% of non CD children reported problems (Table 5).

Regarding parent responses, no significant differences in the dimensions were found across the three groups (Table 5). A greater percentage of parents who had screening-detected children reported problems (3%) in usual activities. Like the children, the group most often reporting problems in the dimension self-care (2%) was comprised of the parents of previously diagnosed CD children. Parents of non CD children most often reported problems in the anxiety/depression dimension (15%). In the dimension pain/discomfort, 18% of the parents of children previously diagnosed with CD and 18% the parents of non CD children reported problems. In the dimension mobility, 1% of both the parents of children with screening-detected CD and the parents of non CD children reported problems (Table 5).
Table 5. Children and parents reporting no problems and problems, by EQ-5D dimensions and across groups, before the children's screening-detected celiac disease diagnosis

*Adapted with permission (Paper II)

There was no difference in VAS scores across groups for either children or parents. The median VAS score in each group for the children was 90, and for parents it was 95.

Gender Aspects

When comparing girls across the three groups (screening-detected, previously diagnosed, and non CD) and boys across the three groups, we found no statistically significant differences between CD status and the dimensions for girls or for boys. However, when girls were compared with boys, we found that within the non CD group more girls than boys reported problems in the dimensions of pain/discomfort (22% compared to 18%, Fisher’s exact test, P=0.001), and anxiety/depression (16% compared to 7%, Fisher’s exact test, P=0.000). Boys in the screening-detected group reported more problems with doing usual activities than girls (7% compared to 0%, Fisher’s exact test, P=0.020).
There was a statistically significant difference in the children's VAS scores related to sex. In the non CD group, which also represents the overall group results, girls reported worse health than boys, with a median score of 90 compared to 93 (independent samples Mann-Whitney U test, P=0.001).

We also found a significant difference in parents' overall reports in the dimensions of usual activity and pain/discomfort with respect to the sex of their child. The parents more often reported problems in the dimension usual activity if their child was a boy (3% compared to 2%, Fisher’s exact test, P=0.001) and in the dimension pain/discomfort if their child was a girl (20% compared to 17%, Fisher’s exact test, P=0.013).
HRQoL at Follow-up

The study described in paper III is the nested case-referent study that includes children’s self-reported health status from baseline (also in Paper II) and at follow-up (1 year later). The health status for the screening-detected (cases) was found to be similar both before and one year after diagnosis (and similar to that of the referents) (Table 6).

Table 6. Adolescents reporting problems (EQ-5D), before and one year after screening-detected celiac disease diagnosis, compared to referents without celiac disease *Adapted with permission (Paper III)

<table>
<thead>
<tr>
<th>Dimensions at Baseline and Follow up</th>
<th>Screening-detected CD (cases n=103) n (%) with problems</th>
<th>Non CD (referents n=483) n (%) with problems</th>
<th>Odds Ratios (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bivariate LR b</td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
<td>Multivariate LR c</td>
</tr>
<tr>
<td>Baseline</td>
<td>3 (2.9)</td>
<td>11 (2.3)</td>
<td>0.78 (0.21-2.84)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1 (1.0)</td>
<td>7 (1.4)</td>
<td>0.67 (0.08-5.48)</td>
</tr>
<tr>
<td>Self care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 0</td>
<td>2 (0.4)</td>
<td>0.00 (0.00-)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0 0</td>
<td>2 (0.4)</td>
<td>0.00 (0.00-)</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3 (2.9)</td>
<td>13 (2.7)</td>
<td>0.92 (0.26-3.30)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2 (1.9)</td>
<td>11 (2.3)</td>
<td>0.85 (0.19-3.89)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21 (20.4)</td>
<td>95 (19.7)</td>
<td>0.96 (0.56-1.62)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>13 (12.6)</td>
<td>106 (21.9)</td>
<td>0.51 (0.28-0.96)</td>
</tr>
<tr>
<td>Anxiety/Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13 (12.6)</td>
<td>52 (10.8)</td>
<td>0.84 (0.44-1.60)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>15 (14.6)</td>
<td>95 (19.7)</td>
<td>0.70 (0.39-1.26)</td>
</tr>
</tbody>
</table>

* Odds ratio (95% confidence interval),
  b Bivariate logistic regression using case/referent and problems reported,
  c Multivariate logistic regression using case/referent and problems reported at baseline and problems reported at follow-up

In the dimension of pain at follow-up, fewer cases reported problems than referents (12.6% and 21.9% respectively, Adjusted Odds Ratio 0.50, 95% CI 0.27-0.94) (Table 6), however, when this dimension was stratified by sex, it was revealed that the difference was between boy cases and referents at follow-up (Table 7).
In the sex stratified results there was a significant difference between the screening-detected and referent boys in the pain dimension at follow-up. Fewer of the screening-detected boys reported problems (4.3%) than the boy referents (18.8%) (Adjusted Odds Ratio 0.17, 95% CI 0.04-0.73) (Table 7).

**Table 7.** Boys and girls reporting problems in pain dimension (EQ-5D), before and one year after screening-detected celiac disease diagnosis, compared to referents without celiac disease *Adapted with permission (Paper III)*

<table>
<thead>
<tr>
<th>Groups at Baseline and Follow-up</th>
<th>Screening-detected CD (cases)</th>
<th>Non CD (referents)</th>
<th>Odds Ratios (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) with problems</td>
<td>n (%) with problems</td>
<td>Bivariate LRb</td>
</tr>
<tr>
<td>Boys</td>
<td>n=47</td>
<td>n=208</td>
<td>1.56 (0.76-3.22)</td>
</tr>
<tr>
<td>Baseline</td>
<td>13 (27.7)</td>
<td>41 (19.7)</td>
<td>0.19 (0.05-0.83)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2 (4.3)</td>
<td>39 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>n=56</td>
<td>n=275</td>
<td>0.68 (0.31-1.53)</td>
</tr>
<tr>
<td>Baseline</td>
<td>8 (14.3)</td>
<td>54 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>11 (19.6)</td>
<td>67 (24.4)</td>
<td>0.76 (0.37-1.55)</td>
</tr>
</tbody>
</table>

*Odds ratio (95% confidence interval)

b Bivariate logistic regression using case/referent and problems reported

* Multivariate logistic regression using case/referent and problems reported at baseline and problems reported at follow-up

Adolescents with screening-detected CD had a median VAS score of 91 at baseline and 90 at follow-up, which was not a significant change (Wilcoxon signed rank test, P=0.916). The referents median VAS score was 90 at baseline and at follow-up. Comparisons of cases and referents at baseline and at follow-up showed no significant differences.

**Gender Aspects**

The finding that fewer of the screening-detected boys compared to the referent boys reported problems with pain at follow-up is further discussed in the gender aspects section in the discussion.

When comparing VAS scores for boys and girls within the case and referent groups, the only significant difference was between the boys and girls in the referent group at follow-up (Mann-Whitney U test, P=0.009), where both report a median of 90 but for the boys and girls the 25th percentile is 85 and 75, respectively, and the 75th percentile is 99 and 97, respectively.
Living with Screening-Detected Celiac Disease (Paper IV)

The narratives written by the screening-detected adolescents reflected a variety of experiences, both at the one- and five-year follow-ups. By focusing on interpreting the experiences unique in the five-year follow-up we aimed to see how perceptions, practices, and beliefs had evolved five years after diagnosis.

Being screening-detected and the length of time the adolescents have lived with CD impacted how they have integrated the disease into their lives. Some have adjusted to the disease and adapted new habits and coping strategies to deal with the GFD. Others still doubt they really have CD or that being detected was beneficial for them. These findings illustrate the importance of providing ongoing support to those with screening-detected CD as they continue to learn about this chronic disease and adapt to the GFD.

The overall theme, *Internalizing the Threat of Risk*, illustrates that these adolescents had internalized the threat of risk, as being detected through screening and the threat of future health complications had impacted how they felt about the diagnosis, coped with the GFD, and thought about CD screening. The theme is supported by four categories: *Maintaining an Imposed Disease Identity*, *Moving from Forced Food Changes to Adapted Diet Routines*, *Enduring Beliefs of Being Spared Negative Consequences*, and *Continuing to Fear it is “all in vain”* (Figure 8).

**Figure 8.** Figure summarizing evolution in perceptions, practices, and beliefs of adolescents after living with screening-detected celiac disease for five years (Paper IV)
Maintaining an Imposed Disease Identity

This category illustrates that these adolescents were continuing to define themselves in relation to the screening. When we compared the narratives for those who had written at both the one-year and five-year follow-ups we saw that the way they described feeling when they got the diagnosis remained constant. They still related how they felt now to their original feelings when diagnosed. Their initial reactions to news of the diagnosis varied and included feeling shocked, feeling like their life had been ruined, feeling relieved, suspecting it, thinking it was not a big deal, and feeling it was unfortunate.

“To be the only one in the whole school who is “different” was among the worst things that I have had happen to me”

“T felt confused and disappointed because my parents had forced me to be with in the study”

“Since then my life has improved considerably. I’m more energetic and have more energy to do more”

They described how it was at home, school, and when away from home. There were a variety of experiences that illustrated how they felt supported or unsupported by others.

“Unfortunate in social situations otherwise intolerance isn’t something that bothers me”

“I usually say that you become “food handicapped”

“Life after was so and so, it felt like I was a burden for everyone”

“The whole family had to change how we think, we became more conscious of what was in the food we eat”

After five years they had had the chance to meet new people and be in new situations where they were identified as having CD right from the beginning. They described that in the beginning they were met with skepticism at school, but after they changed schools (to high school) it was a more comfortable.

“I think it would be good to test everyonel but at a much younger age, maybe the year before you start school so that in some way they will see it is obvious that you eat gluten-free food”
Moving from Forced Food Changes to Adapted Diet Routines

After living with CD for five years the adolescents described habits, routines, coping strategies, and the economic burden of the GFD. Although they still wrote about characteristics of food and certain environments, now they also referred to new food habits and routines, which was a new way for them to reflect. There were a variety of experiences with the GFD. They felt forced to cope, supported, neglected, and stigmatized.

“In the beginning it was difficult, I didn’t know what I could eat, but now it feels natural to have CD”

Another evolution after five years was increased personal responsibility for the GFD. There were also accounts of the financial burden imposed by the diet.

“It became more for me to take responsibility for”

“The biggest change is with my economy”

Enduring Beliefs of Being Spared Negative Consequences

This category reflects that they still believed being diagnosed and following the GFD had spared them from negative health consequences or would do so in the future. The accounts described being motivated to follow the diet in order to avoid developing complications later on. They also gave this as a reason that everyone should be screened, even if they did not feel better and sometimes wondered if a mistake had been made with the diagnosis.

“Sometimes I regret that I was tested-but it was for the best”

“I didn’t suffer eating flour but I definitely think that everyone should be tested, you don’t want to go around being “sick”

“I think all kids should be tested for the simple reason that my life has improved so much that I almost don’t dare think about how life would be today without discovering the gluten intolerance”
Continuing to Fear it is “all in vain”

Even after five years, the children could doubt whether they really had the disease and if they have benefited from the diagnosis. Some said that they quit the GFD and others said that they sometimes chose not to follow it.

“It felt difficult to find out and I have many times thought that it would have been better to be blissfully ignorant”

“For the last 3 months I have eaten regular food to see how the tests will be”

Gender Aspects

When we explored the boys’ and girls’ experiences we found that they were similar, but there were some interesting patterns. The girls were more likely than the boys to describe the overall experience as negative. The boys more often wrote about the adjustment to the diagnosis and diet as nonremarkable. Although the boys gave specific examples of changes they made, the girls were more likely to describe adapting to the GFD as a struggle and mention the financial burden. Most of the adolescents said they followed the GFD; however, the girls were more prone to have quit or not to follow it strictly because they did not notice any benefit.
Discussion

Main Findings

Some of the children who participated in the CD screening experienced fear and anxiety during the screening, but overall they had, or were provided with, tools that allowed them to cope well with the screening. The HRQoL for these screening-detected participants was similar before and one year after diagnosis (and similar to that of the referents). After being detected through the screening, the threat of complications impacted how they felt about the diagnosis, coped with the GFD, and thought about CD screening. Five years after the screening-detected diagnosis the adolescents have adjusted to the disease and adapted new habits and coping strategies to deal with the GFD. However, there are still those who doubt the accuracy and benefit of the diagnosis.

Mass Screening for Celiac Disease

Intervening in Public Health – A Risky Business

Screening attempts to reduce risk yet can also be seen as a “juggernaut” that creates new risks. In the evolution of screening practice and theory, as described previously, screening and associated practices were initially accepted, but as risks were realized mistrust and critique grew.

By reflecting on the history of screening and screening theory it is clear that screening programs must be considered carefully before being implemented. Just like stopping a “juggernaut”, screenings that are implemented and become part of healthcare are difficult to discontinue even if they are not supported by evidence.

A reflective cooperatation between individual, healthcare, and public health interests are necessary to develop a realistic and balanced foundation for screening planning and implementation. Quality assurance measures should also be planned as part of screenings and be ongoing.

This thesis focuses on the perspective of individuals who participated in a CD screening study. By describing what is already known about CD and CD screening and exploring some of the gaps in knowledge related to CD screening (Tables 3a and 3b) some inferences can be made regarding potential impacts a CD mass screening could have on participants.
Participants’ Perspectives

Experts and the public together can make valuable contributions to furthering the understanding of risk (132) and this makes considering the participant perspective especially important when intervening in public health.

The Experience Participating

For the screening participants, the initial screening did not seem to cause excess anxiety. Overall the participants coped well with the screening and felt well informed (Paper I). However; some of the screening-detected participants also participated in focus group discussions one year after diagnosis. They described not really being aware of what the consequences of participating would be (133). We also found that five years after being detected through the screening, some participants expressed that they regretted participating (Paper IV). Most believed that they have avoided future complications; however this may be how they cope living with this chronic disease (97).

HRQoL Before and After Screening-Detected Celiac Disease

When we compared the HRQoL of screening-detected participants before and after diagnosis we did not find a change in the proportion of participants reporting problems, at least up to one year after (Paper III).

Other research that has been done to address how screening, diagnosing, and treating asymptomatic screening-detected individuals affects HRQoL/QoL has mainly involved those with CD who were identified from high risk groups or were compared based on what type of symptoms led to their diagnosis (43, 68, 99-115). In a study that was done with retrospective reporting on the EQ-5D, symptoms of unrecognized CD were associated with a prolonged and substantial reduction in QoL before diagnosis and GFD (99). Likewise, in retrospect after diagnosis and treatment some of the ETICS screening-detected participants reported experiencing symptoms before they had been diagnosed (133). When they were asked to compare how they felt before and one year after diagnosis 54% reported feeling better and 37% reported feeling no difference (133).

A few previous studies have included individuals who could be considered as screened from the general population (2, 116, 134). In those studies, the individuals who had “typical” symptoms showed an improvement in QoL scores after one year on the GFD, while those who were supposedly symptom-free had scores comparable to healthy controls at baseline and at follow-up (116, 134).
These findings (Papers II and II), combined with the findings from the qualitative study done at the time of the screening (Paper I), suggest that screening, diagnosing, and treating CD do not increase the anxiety of the participants, but also shed doubt on the benefit of diagnosis.

**Living with Screening-Detected Celiac Disease**

In the five-year follow-up (Paper IV), the screening-detected adolescents mostly described living with CD as manageable, and they thought that having been diagnosed was positive. There were also some who said that it was the worst thing that had happened to them and a few who had quit the GFD. Other studies have shown that many regard the diet as a burden even after being on it for several years (57, 109, 135-141). In a survey of adults with CD the most common emotion after diagnosis was relief, however, this decreased after starting the GFD (53). Respondents reported feeling frustrated, overwhelmed, and isolated which demonstrates that making lifetime dietary changes can have considerable emotional impact (53). Likewise, the screening-detected adolescents from ETICS, who participated in focus group discussion described feeling like they had to balance the health benefits of adhering to the diet with making social sacrifices (133).

Swedish adults who were clinically-detected as children have been found to still describe dilemmas experienced during adolescence (138). In light of those findings, we could expect that the negative experiences described by the adolescents will remain part of their narrative related to living with CD. On a positive note, when those diagnosed as children reported as adults, they said that now they did not worry about being a burden, being forgotten about, or avoiding disclosure about their CD (138).

These findings highlight some of the complexities related to living with screening-detected CD. In the quantitative studies there was no difference in HRQoL for the screening-detected participants after diagnosis and GFD (Paper III). They also reported a HRQoL similar to their peers both before and after the screening (Paper III). However, by exploring how they felt after diagnosis and treatment using a qualitative approach a more complex picture was discovered. After diagnosis and treatment some of the screening-detected participants described experiencing improvement while others wrote that their lives had become worse (Paper IV).
Living with the Treatment (Gluten-Free Diet)

There were some positive changes related to how the screening-detected participants reflected on the GFD five years after their CD was detected through screening (Paper IV). When they wrote about living with the GFD one year after diagnosis they mostly described the characteristics of the food at home, school, and when out. They described how they were always forced to think about food and plan what to eat. However, after five years they reflected differently and described new food “habits” and “routines” and gave examples of specific strategies used to maintain their GFD (Paper IV). In line with our findings, difficulties and negative emotions were found to be experienced less frequently by adults on the diet for more than five years, although food labelling and eating away from home remained problematic (53).

Another positive transition after five years was that the adolescents described some new environments as better (Paper IV). They met new people or were in new situations where they were identified as having CD right from the beginning, and this resulted in a more comfortable scenario. For example, they were met with skepticism at school in the beginning, but after they changed school (to high school) it became better. The stories one year after diagnosis described being met by cafeteria staff with disbelief and comments such as “a little won’t hurt you”. Five years after diagnosis this seemed to be less of an issue. Perhaps the transition was also difficult for others who struggled to accept the adolescent’s new CD diagnosis and diet limitations. The adolescents and their peers have matured and perhaps they expressed their needs differently and that resulted in positive interactions. They could also have become desensitized to reactions that they had previously experienced as negative.

Compliance with the Gluten-Free Diet

It has been suggested that those who are detected through screening can be at particular risk for poor adherence to the GFD (136). However, one year after diagnosis, 72% of screening-detected adolescents who participated in an ETICS follow-up study reported always eating gluten-free (142). This is similar to the findings in other studies with those diagnosed clinically that show rates for strict adherence from 42 to 96%, depending on definitions and methods of assessment (135, 139-141, 143-144).

Compliance is nuanced. When it comes to children and adolescents, a Canadian study reported compliance at 95% in children (mean age 12) who were clinically-detected (143), but in another study done with 12-year-olds, nine years after diagnosis, almost half had abandoned the GFD (135). A Finnish study has shown that being young at diagnosis and being
a teenager are associated with non-adherence (141). In a qualitative study done with clinically-detected adolescents, non-compliance was discovered to be used as a coping strategy (145). The lack of symptoms or the characteristics of symptoms were described by non-compliers as allowing for flexibility to comply in social situations (145). Such intentional intake of gluten in social situations and when eating take-away food has also been reported by adults (140).

Avoiding immediate reactions to gluten and reducing the risk of long-term complications have been found to be primary motivating factors for adhering to the GFD (53, 139). This is in line with what the screening-detected participants described as reasons for complying with the GFD in Paper IV.
Gender Aspects

In studies involving adults, men and women have been shown to experience the burden of celiac disease differently (53-57). Some of the differences reinforce the notion that gender influences health-related behavior (146-148).

The Experience Participating

When the participants described their experience with screening (Paper I), feelings were expressed more vividly by girls, while boys often expressed feeling indifferent. Boys more often described feeling nervous while waiting for the test results. Other studies have indicated that females are more likely to engage in health promoting behaviors (146), and it might be that the girls in our study felt more comfortable and proud of their participation. The boys’ reluctance to express feelings in relation to the blood test can be related to the gender stereotype that it is not acceptable for men to express feelings, especially of vulnerability (146). It has also been suggested that males fear illness more than females do because it is a threat to their masculinity (146-148), which might explain why boys were nervous while waiting for the results.

Living with Celiac Disease

The finding that fewer screening-detected boys (4.3%) reported problems at follow-up in the dimension of pain than the boy referents (peers without CD) (18.8%) is interesting (Paper III). In a previous Swedish study a twofold greater risk for symptomatic CD in girls compared to boys was found (14), but in this screening study the male to female ratio for those with clinically diagnosed CD was 1:2 compared to 1:1 for those with screening-detected CD (118). This difference reveals that at the time of the screening a larger proportion of girls compared to boys had already been diagnosed with CD in routine clinical practice (118). It could be that the boys with unrecognized CD were further progressed in their disease at baseline because they were not as likely as the girls to have been detected in clinical practice. One could speculate that even though they may not have realized the extent of their problems at baseline, they experienced benefit from the treatment resulting in fewer of these boys reporting problems with pain than the boys in the referent group, a phenomenon that was not captured for the girls. Studies have also shown that men and women access healthcare differently (146-148). Perhaps the boys were less likely to seek or receive care. It is also possible that clinicians expect girls to have a higher risk of developing CD and more readily recognize and diagnose girls.
The boys and girls in the follow-up study, five years after the screening-detected CD diagnosis (Paper IV), had similar experiences but with some different patterns. The girls were more likely to describe the overall experience as negative. Other studies with adult women with CD have reported similar findings. One study found that adult women with CD experienced emotional distress related to the GFD more than men (53). Women with CD have also been shown to experience the disease as more of a burden than men (54-57). Our findings illustrate that the adolescents experienced some burden related to the diagnosis and adaptation to the GFD, and even more so for the girls (Paper IV). The screening-detected boys wrote about adjustment to the diagnosis and diet as something they just did (Paper IV). Boys were prone to give specific examples of changes they made, while girls were more likely to describe the struggle to adapt, the financial burden of the diet, or that they had quit the diet when they did not experience benefit. These findings are in line with what has been found in adults where it has been shown that men with CD used problem-orientated methods to cope, while women sought emotionally oriented strategies and ultimately showed less satisfaction with the outcome and more distress due to the daily restrictions in their lives (57).

Further investigation was done to explore the situation with the boys who had reported problems with pain on the EQ-5D (Paper III). After the narratives from the five-year follow-up were collected three boys who reported problems with pain and who had also submitted narratives were identified. One of these boys had also reported problems with pain at the time of the screening. In his narrative written at the one-year follow-up he said, “It was really unfortunate that life had to change”. At the five-year follow-up he wrote that he had stopped eating gluten-free three months before his scheduled visit with the doctor in order to “see how the tests would be”. Another boy described that he felt pressure to feel better. The third boy that reported problems with pain and also wrote a narrative said being diagnosed was the worst decision in his life up until now.

These aspects related to gender, CD, and CD screenings suggest that attention should be given to the differences in how healthcare approaches females and males. It also shows that how females and males cope with CD and the lifestyle changes after diagnosis are different and tailored ongoing support could be beneficial.
Moving Forward

Part of screening history and theory have been presented to pave the way for discussing what is known and what is left to be learned about CD and CD screening.

If mass screening was implemented as a public health intervention, screening during childhood could be a strategy. The pediatric primary care setting has been suggested as a venue for delivering screening (77). Usually a functional infrastructure is already in place when it comes to children (e.g. school, routine health checks, vaccination programs), whereas introducing screening interventions among adults has proved to be more problematic (79). The benefit from screening may be more obvious in early life, because complications related to the ongoing malabsorption and inflammation may negatively impact childhood growth and development (41). The children who participated in the screening did not experience excess anxiety (Papers I and II), however they may experience false reassurance because they could still develop CD later in life (4, 20). If screening is undertaken during childhood or adolescence the best age for screening and the issue of follow-up screenings must be clarified. Also, if screening is done during childhood or adolescence special consideration should be given to their perceptions of risk, autonomy, and the issue of informed consent (73, 149).

Individuals must have, or be provided with, the resources and support needed to understand the disease and maintain the diet. The healthcare sector must have the resources and capacity to meet the needs of all the individuals who want to be tested for CD, need medical consultation and information, require diagnostic biopsies, and need professional dietary counseling.

In order to maximize the benefit there should be a high detection rate for finding cases and high acceptance rates for the intervention (72). To minimize harm there should be a low false positive rate and the opportunity for the participants to understand what is being offered and to think carefully about whether participation is right for them (72). It must also be certain that cases picked up would have developed serious disease if they had not been identified and that earlier detection improved the outcome (72).
Uncertainties Remain

Because inflammation is present in those with unrecognized CD there are probably negative health consequences, even if the individual may consider themselves symptom-free (8, 47, 150-151). Compliance to the GFD usually results in intestinal recovery and the serological markers indicative of the intestinal damage and inflammation usually revert to normal levels (20). Symptoms and most of the physical consequences caused by the disease most often resolve (37). However, the impact of consequences during the period that the CD is untreated are unclear (4, 20). Screening-detected individuals usually haven’t sought help for symptoms and it is not safe to assume that being detected has improved their health. For those with unrecognized CD it is possible that they could have managed without noticing symptoms or negative health consequences for an undefined amount of time.

There are economical burdens for individuals and the healthcare system associated with unrecognized CD (50, 152-154). The current evidence on the cost-effectiveness of mass screening for CD is contradictory (155-158). One study found: 1) time delay from symptom onset to diagnosis, 2) adhering to the GFD, and 3) the prevalence of CD had the largest impact on cost-effectiveness and they suggested that CD mass screening could be cost-effective (156). Another study that compared the cost-effectiveness of mass screening to screening those with symptoms or at high risk within routine practice found that CD screening practiced in routine healthcare was most effective (157). In the ETICS study the estimated cost was 47 Euros (~64 United States Dollars) per child screened (159). Currently a study is underway to compare the costs of a screening and nonscreening scenario using QALYs that will utilize the HRQoL data of the ETICS adolescents.

Other Options for Finding Celiac Disease

In Sweden, there is no national screening policy only recommendations and guidance for specific procedures. Regional and local governments (County Councils) are responsible for their local screening policy and implementation (78). Recommended intervals for screening, what age groups to include, and the quality controls applied differs from county to county (78). There are national recommendations for screening for breast and cervical cancer and the County Councils are responsible for overseeing these (78). Screening for pregnant women, antenatal screening of the fetus, and screening of newborns and children are part of routine healthcare that is free of charge for the recipients (160). Screenings that are currently under debate in Sweden include screening for abdominal aortic aneurysm, colorectal cancer, and prostate cancer in men (78, 161-162). Policy for the mass screening of CD does not exist and therefore CD is currently diagnosed through routine healthcare.
There are also options besides mass screening for dealing with unrecognized CD. Another option to identify those with unrecognized CD could be to work towards an increased awareness among the population and practitioners in order to improve the capability to recognize symptoms and diagnose CD. Those who are clinically-detected have been found through routine healthcare which involves testing when symptoms raise suspicions or because that individual is considered at high risk. However, this seems unlikely to identify all of those with unrecognized CD. The findings described in Papers II and III showed that asking the general population about health does not separate those with unrecognized CD from their peers. Another study, involving screening-detected ETICS children, focused on asking the population about physical symptoms and high risk factors. In line with our findings (Papers II and III), that study found that those with unrecognized CD would not have been found by asking about symptoms (163).

Another option would be for public health interests to focus on working with industry that manufactures and markets self-test kits. Perhaps public health advocates should offer guidance on how to market and instruct use on self-test kits or advocate for regulation.

Finally, detection within routine healthcare when those with unrecognized CD present with symptoms could be continued as the standard practice. However, the delay to diagnosis is long and has been shown to be around 9-11 years (67-68). One study with Swedish adults, showed a six year delay between when care was sought for CD related symptoms and a confirmed diagnosis (68). While a diagnosis is being sought, consequences of the disease and the utilization of healthcare services can be costly (50, 152-158).
Methodological Considerations

Reflective of Mass Screening Scenario

Other research that claims to be representative of screening-detected individuals is usually based on persons who are tested and diagnosed because they have been considered at an increased risk for CD. This type of screening is actually selective, i.e., screening of certain high-risk groups in the population (75). Selective screening can be one form of population screening, but it should not be considered the same as mass screening. Setting out clear and consistent definitions matters, especially if we are to base health policy and practice on current evidence.

A strength of these studies is the fact that the adolescents had their CD detected as a result of a population-based screening study, not clinically or because they were considered at high risk. Our results are more reflective of all those living with unrecognized CD, and the lack of this research has been seen as a limitation (2).

Another strength is that data was collected from the participants before they knew of their diagnosis (Papers I-III). Being able to present data from before the individuals knew of their CD diagnosis is unique and differs from studies in which individuals are asked to recall how they felt at the time of their diagnosis.

Also, in the studies described in Papers II and III data was collected from and compared with other 12-year-olds from the same ETICS population and this strengthens the interpretations of the results.

Screening “Study”

The children were aware that the CD screening was part of a study, this cannot be completely separated from the children’s screening experience.

The idea that there would be a greater benefit, and not just a benefit for themselves, could have motivated participation. The children who participated felt like they were being good citizens (Paper I). Also, in this Swedish context, children have the right to free healthcare and treatment. The children who participated in this screening study assumed that individuals would be treated fairly and have access to treatment (Paper I). These factors could have affected the children’s experiences in a way that routine screening would not and should be considered when applying findings to other contexts.
Nonparticipants are Important

These studies only included those who agreed to take part in ETICS. In the first field phase of ETICS 10,041 children were invited and 75% agreed to participate, whereof 7,208 (72%) had CD serological markers analyzed (6). Even though a 72% participation rate is usually considered acceptable, the nonparticipants’ contributions would be valuable.

We can assume that some of the nonparticipants choose not to be involved because of the required blood sampling. Indeed, many children who did participate were anxious about this (Paper I). Measures such as mailed and telephoned reminders to those who who had not sent back consent forms were carried out to maximize participation. There are also some who missed school on the day of sampling or missed receiving the invitation.

Those who decided not to participate may be the ones who were most anxious about the screening or had the poorest HRQoL. Those who declined participation could also have an interesting and contradictory view on screening for disease. They may believe it unnecessary to find a disease they do not suffer from, they may doubt they will be treated well, or they may lack the resources to foresee a lifestyle change as possible. We realize that these individuals could have a valuable contribution; however, they had declined participation and we did not contact them again.

Written Narratives

Narratives are “stories” of events that people organize to convey meaning and the subjective nature of them are what allowed us to understand the participants’ reality (91). Being able to capture experiences through narratives is positive, but there are also potential drawbacks when using this method. Because these participants are often required to write in school, we expected writing essay like stories to be a method that they were comfortable with, but there are different skill levels in writing that may have affected the depth and length of the narratives. The written narrative method only allows us to glean information from what the participant provides. If we had conducted interviews or focus group discussions it may have been possible to probe deeper about specific issues.

In order to increase the trustworthiness of the qualitative studies (Papers I and IV) the researchers involved were from varying disciplines (interdisciplinary triangulation) and contributed with expertise in CD research, pediatric medicine, qualitative research, and nursing practice. There were frequent discussions and peer debriefing throughout.
To increase validity and ensure that the results were grounded in the narratives, there was continuous comparison of the codes, categories, and the theme back to the narratives.

**EQ-5D**

We used the “Swedish child-friendly pilot version of the EQ-5D instrument”, which is a generic tool used to describe HRQoL (Papers II and III) (122, 127). This tool was also included in the questionnaire in order to make it possible to carry out a future health economic evaluation using QALYs. A strength of this instrument is that the participants report their own valuation of their health. Also, the tool has been tested and is considered age appropriate. Due to the size of the non CD group, their results are representative of the overall group and because our study is based on a cross-sectional screening, the results are also representative for the general Swedish population in this age group and similar to findings that have been reported in other studies (123, 164-165).

Even though the EQ-5D instrument is a validated tool and we used the “Swedish child-friendly pilot version”, this tool may have limitations in the context of this study. Perhaps it is not the ideal tool for capturing subtle problems or feelings caused by unrecognized CD. Also, these adolescents may have adapted to their current health situation as being normal, and at baseline they may have rated their health status as high as possible, similar to their peers, and problem-free. If they did experience improvement after diagnosis and treatment, they would be unable to demonstrate improvement from the high health status previously reported.
Concluding Remarks

Within this context some inferences can be made regarding potential impact of mass screening for CD. Our findings suggest that it is possible for participants to avoid excess anxiety during CD screening. However, there was not consensus among participants that being detected and treated had improved their HRQoL or that the immediate benefits outweighed the harm caused by being detected in this way.

When considering mass screening, the affect on the participants is important to take into account and our findings shed light on some of the potential impacts a CD mass screening could have on participants if implemented as a public health intervention.

Future Considerations

There is still more to be learned in regards to mass screening for CD including; at what age a screening would be most appropriate, what the natural health consequences of untreated CD are, and what the health economic impact of such a screening would be. Also, evidence from nonparticipants would deepen the understanding of how the population feels about screening in general and screening for CD in particular. These issues should be considered further before a CD mass screening “juggernaut” is unleashed as a public health intervention.

Researcher’s Reflections

While working as a nurse in a variety of settings, I have seen first hand how altered health affects individuals. This has fueled my interest in public health and intervention evaluation from the participant perspective. The impetus for my doctoral education was my involvement in a celiac disease screening study. I was involved in fieldwork and assisted research nurses in local schools. This is when I met and interacted with the participants. This experience allowed for me to meet and observe the children being screened and also gain insight into the sampling and protocol procedures. The fieldwork and PhD study process has led me to appreciate the complexity of intervening in public health. Translational research that will best meet the needs of the population while also placing value in holistic care of the individual is what I have aimed to achieve.
Acknowledgements

As I think back on my time as a PhD student, at the Epidemiology and Global Health Unit, and in Umeå there are many people who have been important to me. I am grateful to have been a part of such a rich and warm environment and for all those who have made this process special.

Thank you to all the children and their families who participated in ETICS and the follow-up studies. To me the best outcome would be if your voices were heard and participant perspectives always played a vital role in the discussion and planning of health interventions.

Thank you to my supervisor, Anneli for the many years of optimistic support, motivation, and being an enthusiastic mentor. Thank you to my co-supervisors; Maria for giving me such an insightful glimpse into the world of qualitative research and Lund and to Lars for contributing the calm and steady on an occasionally bumpy ride.

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I am lucky to have found myself in the midst of exceptional coworkers within the ETICS project. Thanks to everyone who was a part of the "ETICS gang", all of the site doctors and nurses, nutritionists, gender experts, etc. for showing interest and support whenever we met. A special thanks to Ruth Gerd and Maria F. for allowing me the assist during the fieldwork.

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Bakgrund och syfte med avhandlingen  Celiaki, även kallad glutenintolerans, är en kronisk sjukdom. Personer med celiaki får skador i tunntarmens slemhinna om de äter livsmedel som innehåller gluten. Prevalensen varierar varierar från cirka 1-3%, men de flesta med celiaki är fortfarande odiagnostiserade. En möjlighet för att hitta merparten med celiaki vore en allmän screening, d.v.s. mass-testing av befolkningen. En allmän screening skulle innebära att personer som tror sig vara friska får veta att de lider av denna livslånga sjukdomen. Innan en sådan intervention kan övertygas måste effekterna, båda positiva och negativa av testning och diagnostiserande ha beforskats. Syftet med denna avhandling är att undersöka möjliga effekter av en allmän testning för celiaki genom att utforska upplevelser och utfall hos personer som deltagit i en sådan studie.

Metoder och Deltagare  Både kvalitativa (korta skriftliga berättelser) och kvantitativa metoder (frågeformulär med EQ-5D instrumentet) användes i datainsamlingen Barn som deltog i screeningen inbjöds att skriva berättelser vid tidpunkten för blodprovtagning, innan dess resultat var kända (n=240). EQ-5D instrumentet användes för att mäta och jämföra hälsorelaterade livskvalité vid tiden för screeningen och ett år efter screeningen (screening-upptäckt n=103, referenter n=483). De med screening-upptäckt celiaki uppmunades också att skriva berättelser ett och fem år efter diagnosen. I dessa berättelser beskrev ungdomarna hur det kändes att få diagnosen, hur det känns att leva med celiaki, och vad de tycker om en framtidlig screening för celiaki (ett års uppföljning n=91, fem års uppföljning n=72).

Resultat  Även om vissa barn kände rädsla och oro under screeningen så hade de verktyg som tillät dem att klara av screeningen på ett bra sätt. Det var ingen skillnad i hälsorelaterade livskvalité hos dem med screening-upptäckt celiaki före och ett år efter diagnos (och inte heller då man jämförde med referenterna). Vi fann också att efter att ha levit fem år med diagnosen, hade det varit en utveckling för dessa ungdomar. Att få sin celiaki diagnosticerad via en screening och rädslan för framtidlig komplikationer påverkade hur de kände för diagnosen, klarade av glutenfri kost, och vad dem tycker om celiakiscreening.

Slutsatser  Våra resultat visar att det är möjligt att genomföra celiakiscreening utan att skapa onödig oro, men deltagarna var inte eniga om att diagnosen och behandlingen hade förbättrat deras hälsorelaterade livskvalité eller att fördelarna uppvägde de nackdelar som orsakats av att sjukdomen upptäckas på detta sätt. När man överväger att införa massundersökning genom screening, måste man beakta deltagarnas upplevelser och våra resultat visar på potentiella effekter för deltagarna.
References


Appendices

Appendix 1. Invitation letter sent home (A small booklet with English and Arabic translations available on ETICS web site: http://www9.umu.se/phmed/epidemi/celiaki/etics/parchild.htm)

Dear parents!

Your child is invited to participate in a study about gluten intolerance.

The study’s purpose is to investigate how common gluten intolerance is and if there is a way to prevent the disease. Therefore 10,000 children in the 6th grade, from different parts of Sweden, will be included in the study.

Gluten intolerance, also known as celiac disease, is a common disease in which the intestine is injured by gluten, a substance naturally found in wheat, rye, and barley. The symptoms can vary greatly and can be anything from obvious stomach problems to general fatigue. The occurrence of gluten intolerance is often compared to an iceberg, which partly lies under the water and isn’t seen, because many can have the disease without realizing it.

The study is called ETICS- Exploring the Iceberg of Celiacs in Sweden and is approved by the Research Ethics Committee.
Study specifics

The study will be conducted some time during the 6th graders’ school year. The class will visit the school nurse where each child will be weighed, have their height measured, and give a simple blood sample. The sample requires only a small amount of blood and numbing gel can be used.

The blood sample is analyzed for markers that indicate gluten intolerance and other markers that can occur with the disease. All families will be contacted with the results from the blood test for their child. If gluten intolerance is suspected an invitation for a visit to a pediatrician at the nearest hospital will be offered.

During a lecture the children will fill out a questionnaire regarding how they feel and what they think about being involved in the study. We will also ask you to fill in a questionnaire regarding your child’s health.

Advantages and disadvantages with participating

An advantage is that you will recieve an answer if your child has gluten intolerance or not. There is much to gain if you discover the disease. Treatment, which includes a gluten free diet, is enough that most feel fine and also decreases the risk of susequent disease. By participating in this study you and your child will gain valuable insight about the public health problem that gluten intolerance is.

A disadvantage is that some lecture time will be lost, approximately one hour. There can be some short-term discomfort when the blood sample is taken, although for the most part this can be avoided by using the numbing gel. Waiting for the result of the blood test can also mean anxiety for you as a parent.

Gluten intolerance is studied, among other things, by examining the blood samples for one or more of the markers of the disease (for example tissue transglutaminase and HLA DQ2/DQ8) and some even for thyroid and pancrease related antibodies. We will also analyze the children’s height and weight development along with their pain experience.
Your child can only participate if you give your permission. You can do this by completing the enclosed form that can be sent to the school.

Participation is by free will. You and your child can discontinue participation at any time without question.

More information: [http://www.umu.se/phmed/epidemi/celiaki/etics](http://www.umu.se/phmed/epidemi/celiaki/etics). You are welcome to contact us if you have any questions! Call any of us directly or contact our coordinator Barbro Skog by telephone at 090-785 12 10. We can also be contacted via email at the address: etics@epiph.umu.se.

*We hope your child will participate!* By being involved in this study you contribute valuable insight that can benefit many children in the future.

*Best Regards*

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As with other healthcare agencies/facilities we have a strict privacy policy. The tests are handled according to the biobank laws. All information in the study will be collected in a database that will follow Swedish privacy laws ("personuppgiftslagen"). The address where the database will be kept is: Epidemiologi and Folkhälsovetskap, Institutionen för Folkhålsa och Klinisk Medicin, Umeå Universitet. The contact person is Anneli Ivarsson.
Gluten intolerance – some facts

Gluten intolerance, also known as celiac disease, is a disease in which a person can’t tolerate the gluten that is naturally found in the grains of wheat, rye, and barley. The gluten injures the lining of the intestine which prevents nutrients from being absorbed by the body as they normally would.

Gluten intolerance can cause many different problems. Symptoms are often more obvious in small children, noticed most commonly are diarrhea or constipation, and can sometimes lead to abnormal growth. Older children, who grow normally despite the disease, often have vague symptoms such as general fatigue. Other problems that can develop are delayed puberty, anemia, nutritional deficiencies, bone fragility, depression, and a long list of other health problems. People with untreated gluten intolerance also have an increased risk for some autoimmune diseases such as diabetes and thyroid disease.

Gluten intolerance is often undiagnosed because symptoms can be vague and differ greatly from person to person. In addition symptoms can vary for a person during their life time. Also if a person has had the disease for a long time they may have gotten used to not really feeling well. One can even have gluten intolerance without experiencing any symptoms and not develop health problems until later in life.

Gluten intolerance is identified through a blood test that analyzes markers indicative of the disease. In order to confirm the diagnosis a biopsy of the small intestine is performed. Treatment of the disease involves refraining from all food that contains wheat, rye, or barley.

A Gluten free diet is not something a person should try on their own! It is important to first meet with a doctor and dietician for examination as well as diet advice. If gluten intolerance is diagnosed a gluten free diet should be followed in the future, which will result in one feeling better and having more energy to function.
Greetings to you in the 6th grade!

You are invited to participate in a study dealing with the disease of gluten intolerance. 10,000 children from the 6th grade, from different parts of Sweden, are invited to participate in this study.

How does this study work?

At some time, while you’re in the 6th grade, you and your classmates will visit the school nurse. There you will be weighed, have your height measured, and give a simple blood sample. You may receive numbing gel before the blood sample if you want to. In the classroom you will be able to answer a questionnaire about how you feel.

The bloodsample is later analyzed in a laboratory. If we suspect that you could have gluten intolerance we will contact you and your parent/s. Then you will be able to visit a doctor.

Participation is by your own free will! If you feel unsure about something, talk to your parent/s.
ETICS – a study about gluten intolerance

We would appreciate it if You would send the completed form to the school regardless of what you have answered!

Our hope is that all children participate, even those that are already diagnosed with gluten intolerance.

I give permission for my child to participate in the study  
| Yes ☐ | No ☐ |

My child has already been diagnosed with gluten intolerance  
| Yes ☐ | No ☐ |

My child already follows a gluten free diet  
| Yes ☐ | No ☐ |

Child’s name  
| …………………………………………………………………… |
| First name |

| …………………………………………………………………… |
| Last name |

Personal ID number  
| …………………………………………………………………… |

School/class  
| …………………………………………………………………… | ……………. |
| School | Class |

Homeaddress  
| …………………………………………………………………… |
| Street address |

| ……………………… | ……………………… |
| Post number | neighborhood / locality |
Telephone & e-mail

Home telephone

Parent’s daytime telephone

Parent’s e-mail

Date

Signature

Printed name

Signature

Printed name

Thank you for your help!
Appendix 2. Writing instructions for short written narratives used in study described in Paper I

**Hey, you in 6th grade!**

Thanks that you want to tell us about *your experience* participating in the study on gluten intolerance.

Remember that there is no right or wrong because it is *your experience* we are interested in.

- Begin by writing your name and class
- Your story can be written in the way that suits you best but we would like it if you include some of the points below:
  - *How did it go and how did you feel when you decided to be with?*
  - *How did it go and how did you feel the day the blood test was taken?*
  - *How did it feel when you waited for the results of the blood test?*
  - *Also describe what you think is important to think about in the future when children are with a study like this.*
- Put the story in the envelope and seal it. No one will see what you have answered, except those who work with the study.
- Turn in the envelope so that you can be checked of the list.

*Thanks for telling us!*
Appendix 3. Writing instructions for short written narratives used in studies described in Paper IV

You know best what it is like to have gluten intolerance!

That is why we would appreciate if you write about your experience with it. You can write in whatever way suits you, but please address some of the points below:

- How did it feel to find out you had gluten intolerance?
- Did life change after you found out you had gluten intolerance?
- How does it work with food at home and in school?
- Do you think it would be good to test all kids for gluten intolerance and if so, how old do you think one should be when tested?
Appendix 4. “Swedish child-friendly pilot version of EQ-5D” used in studies described in Papers II and III

DIN HÄLSA IDAG

Hur är din hälsa?
Kryssa i den ruta i varje grupp som bäst beskriver hur din hälsa är idag.

Kunna röra sig
- Jag går utan svårigheter
- Jag har lite svårt att gå
- Jag har mycket svårt att gå

Ta hand om sig själv
- Jag behöver ingen hjälp med att tvätta mig eller klä på mig själv
- Jag har lite svårt att tvätta mig eller klä på mig själv
- Jag kan inte tvätta mig eller klä på mig själv

Göra vanliga aktiviteter
(till exempel det du brukar göra på dagarna: gå i skolan, familje- och fritidsaktiviteter, hobbys, sportaktiviteter, lek)
- Jag kan göra mina vanliga aktiviteter
- Jag har lite svårt att göra mina vanliga aktiviteter
- Jag kan inte göra mina vanliga aktiviteter

Ha ont eller ha besvär
- Jag har inte ont eller några besvär
- Jag har lite ont eller lite besvär
- Jag har mycket ont eller mycket besvär

Känna sig orolig eller ledsen
- Jag känner mig inte orolig eller ledsen
- Jag känner mig lite orolig eller lite ledsen
- Jag känner mig mycket orolig eller mycket ledsen
Hur bra eller dålig är din hälsa i dag?

- På skalan är 100 den bästa hälsa du kan tänka dig.
- På skalan är 0 den sämsta hälsa du kan tänka dig.
- Rita en linje från den gråa rutan till den punkt på skalan som visar hur bra eller dålig din hälsa är i dag.
- Fyll sedan i det värde som du valt på termometern i rutorna här nedanför.
Appendix 5. EQ-5D-Y English version that the “Swedish child-friendly pilot version of EQ-5D”, used in studies described in Papers II and III, is based on

<table>
<thead>
<tr>
<th>EQ-5D-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Describing your health TODAY</strong></td>
</tr>
</tbody>
</table>

Under each heading, please tick the ONE box that best describes your health TODAY

**Mobility (walking about)**
- I have **no** problems walking about
- I have **some** problems walking about
- I have **a lot** of problems walking about

**Looking after myself**
- I have **no** problems washing or dressing myself
- I have **some** problems washing or dressing myself
- I have **a lot** of problems washing or dressing myself

**Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)**
- I have **no** problems doing my usual activities
- I have **some** problems doing my usual activities
- I have **a lot** of problems doing my usual activities

**Having pain or discomfort**
- I have **no** pain or discomfort
- I have **some** pain or discomfort
- I have **a lot** of pain or discomfort

**Feeling worried, sad or unhappy**
- I am **not** worried, sad or unhappy
- I am **a bit** worried, sad or unhappy
- I am **very** worried, sad or unhappy

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- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.