Mass screening for celiac disease in 12-year-olds

Finding them and then what?

Anna Rosén
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“It’s good to know, so that you don’t get sick from it in the future”

Boy, sieved out in a celiac disease screening
# Table of contents

**Table of contents** ........................................................................... i

**Abstract** .................................................................................. iv

**List of abbreviations** ............................................................ vi

**Original papers** ....................................................................... vii

**Introduction** ............................................................................... 1
  Mass screening as a public health intervention ..................... 1
  What screening tests are offered to Swedes today? .................... 4

**Celiac disease** ............................................................................. 5
  Increasing occurrence of celiac disease ................................. 5
  Etiology ....................................................................................... 5
  Clinical presentation ............................................................... 6
  Diagnostics ................................................................................ 6
  Treatment .................................................................................... 7
  Treatment’s impact on quality of life ........................................ 8
  Associated conditions ............................................................ 9

**Has the time come for mass screening for celiac disease?** 10
  Finding celiac disease in a mass screening ............................ 10
  Consequences of being found in a mass screening .................. 11

**Aims** ........................................................................................ 12

**Material and methods** ............................................................. 13
  Study context .............................................................................. 13
  The screening ............................................................................. 14
  Participants: children or adolescents? .................................... 16

**An emergent multi-methodological approach** ....................... 17

**Finding undiagnosed celiac disease (Papers 1 and 2)** .... 19
  Participants ............................................................................... 19
  Data sources .............................................................................. 20
  Analytical approach ............................................................... 23

**Experiences of receiving the diagnosis (Papers 3 and 4)** .... 25
  Participants ............................................................................... 25
  Data sources .............................................................................. 27
  Qualitative analytical approach ............................................. 31
Comparing children’s and parents’ responses (Thesis)...... 33
Participants .................................................................................................. 33
Data sources ................................................................................................. 33
Analytical approaches .................................................................................. 34
Ethical considerations ................................................................................ 35

Results ........................................................................................................ 36

Strategies for finding undiagnosed celiac disease ............ 36
Asking children for CD-associated symptoms (Paper 1) ............... 36
Asking parents for CD-associated conditions (Paper 1) .......... 38
Asking children and parents for CD-associated symptoms and
conditions (Paper 1) .................................................................................. 40
Analyses of serological and genetic markers (Paper 2).............. 41

Experiences of receiving the diagnosis ........................................ 43
Reasoning behind participation (Paper 4).............................................. 44
Immediate reaction to the diagnosis (Paper 4) .................... 45
Changes in perceived health (Paper 3) ................................................. 47
Living with celiac disease (Paper 3) ....................................................... 48
Looking back at the screening (Paper 4) .............................................. 51
Attitudes towards future screening (Paper 4) ..................................... 53

Comparing children’s and parents’ responses ................... 55
Recognition of symptoms before diagnosis (Paper 3 and thesis) .... 55
Compliance with the gluten-free diet (Thesis) .................... 57
Change in wellbeing (Thesis) ................................................................. 58

Methodological considerations ............................................... 59
Strengths ..................................................................................................... 59
Limitations .................................................................................................. 60

Discussion ................................................................................................. 63
Main findings ............................................................................................... 63
How to find undiagnosed celiac disease? .................... 64
Experiences of receiving a diagnosis in a screening ............ 67
Invited and sieved out .............................................................................. 67
Perceived health before diagnosis ......................................................... 68
Impact on quality of life ........................................................................... 69
Acceptability of a mass screening .......................................................... 70
Who holds the truth? .............................................................................. 71
Should celiac disease be added to the list of diseases screened for in the general population of Sweden?......... 72

Concluding remarks and future prospectives .................. 77

Personal reflections from the researcher .................... 80

Svensk sammanfattning ................................................. 82
  Bakgrund till och syfte med avhandlingen .......................... 82
  Deltagare och metod .............................................. 83
  Resultat ............................................................ 83
  Slutsatser .......................................................... 84

Acknowledgements .................................................. 85

References .................................................................. 89
Abstract

Background Mass screening for celiac disease (CD) as a public health intervention is controversial. Before implementation, a suitable screening strategy should be outlined, and the acceptability of the screening scrutinized. Also, the benefits of early detection and possible negative consequences should be explored and compared. The overall aim of this thesis was to evaluate different strategies for finding 12-year-olds with undiagnosed CD in the general population, and to explore the experiences of those receiving the diagnosis in a mass screening.

Methods A school-based CD screening of 12-year-olds was conducted in five study sites across Sweden. Out of 10041 children who were invited, 7208 had a blood sample analyzed for CD-marker tissue transglutaminase of isotype IgA (tTG-IgA) and 7161 for total serum IgA (s-IgA). If the s-IgA value was low, tTG-IgG was also measured. Additional analysis of endomysial antibodies (EMA) was performed if borderline values of tTG were found. In total, 192 had elevated CD-markers, 184 underwent a small intestinal biopsy and 153 eventually had CD diagnosed. Before receiving knowledge about their CD status, children and their parents filled in questionnaires regarding symptoms and CD-associated conditions. Questionnaires were returned by 7054 children (98%) and 6294 parents (88%).

Later, all adolescents who had been diagnosed with CD more than one year ago (n=145), and their parents, were invited to a mixed-method follow-up study in which they shared their experiences in questionnaires, written narratives and focus group discussions. In total, we have information on 117 (81%) of these adolescents, either from the adolescents themselves (n=101) and/or from their parent/s (n=125). Data were analyzed using a combination of descriptive and analytical quantitative and qualitative methodologies.

Results We found that information on symptoms and CD-associated conditions were poor predictors for finding undiagnosed CD in the study population. Questionnaire-based case-finding by asking for CD-associated symptoms and conditions would have identified 52 cases (38% of all cases) at a cost of blood-sampling 2282 children (37% of the study population). The tTG-IgA test had an excellent diagnostic accuracy with the area under the receiver operating characteristic curve of 0.988. If using the recommended cut-off for tTG-IgA (>5 U/mL) 151 had fulfilled biopsy criteria and 134 CD cases had been
identified. The strategy of lowering the cut-off to tTG-IgA>4 U/mL, and adding the EMA analysis in those with tTG-IgA between 2-4 U/mL, identified another 17 cases (a 12% increase) at the cost of performing 32 additional biopsies. Measuring total s-IgA in 7161 children discovered only two additional cases at the cost of performing 5 additional biopsies. The positive predictive value of our screening strategy was 80%.

Results from the follow-up study of the screening-detected CD cases illustrated that 54% reported health improvement after initiated treatment, but also that these health benefits had to be balanced against social sacrifices. We also found that although the screening-detected diagnosis was met with surprise and anxiety, the adolescents and their parents were grateful for being made aware of the diagnosis. A majority of parents (92%) welcomed a future screening, but both adolescents and parents suggested that it should be conducted earlier in life.

**Conclusion** Obtaining information on symptoms and CD-associated conditions was not a useful step in finding undiagnosed CD cases in a general population. The serological marker tTG-IgA, however, had excellent diagnostic accuracy also when lowering the cut-off. The diagnosis had varying impact on adolescents’ quality of life, and their perceived change in health had to be balanced against the social sacrifices resulting from the diagnosis. Overall, CD mass screening seemed acceptable to most of those who were diagnosed and their parents.
### List of abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CD</td>
<td>Celiac disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>EMA</td>
<td>Endomysial antibodies</td>
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<td>ESPGHAN</td>
<td>European Society of Pediatric Gastroenterology and Hepatology Association</td>
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<td>ETICS</td>
<td>Exploring The Iceberg of Celiacs In Sweden</td>
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<td>FGD</td>
<td>Focus group discussions</td>
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<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>IgA</td>
<td>Immunoglobulin A</td>
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<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>ROC curve</td>
<td>Receiver Operating Characteristic curve</td>
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<td>tTG</td>
<td>Tissue transglutaminase</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Original papers

**Paper 1:** Anna Rosén, Olof Sandström, Annelie Carlsson, Lotta Högberg, Ola Olén, Hans Stenlund, Anneli Ivarsson. Symptoms do not predict celiac disease in a mass screening of Swedish 12-year-olds. *Submitted*

**Paper 2:** Olof Sandström, Anna Rosén, Carina Lagerqvist, Annelie Carlsson, Olle Hernell, Lotta Högberg, Anneli Ivarsson. Transglutaminase IgA antibodies in a Swedish celiac disease mass screening and the role of HLA-DQ genotyping and endomysial antibodies in sequential testing. *Submitted*


Introduction
From being considered a rare disease mostly affecting children of European origin, celiac disease (CD) has now emerged as a common disorder, present all over the world and with an onset in all ages. The majority of CD cases are undiagnosed and there is a call for increased awareness of the disease, with intensified active case-finding strategies, or possibly even mass screening, to find the cases.

Mass screening for CD, actively seeking the condition in the general population, offers an option for finding the majority of cases. But how would such mass screening be conducted? Which screening tools should be used? How would a mass screening affect those who get their CD detected? And what are their experiences of being found? These issues are what this thesis is about.

Mass screening as a public health intervention
Regulated by Swedish law, the aim of health care is good health and care on equal terms for the whole population (1). It is stated in this same regulation that health care shall offer the means to medically prevent, investigate, and treat diseases and injuries.

Initiation of a medical investigation and/or treatment most commonly results from a clinical visit requested by the patient who is seeking help for symptoms from which he or she is suffering. If a diagnosis is found, the disease is already manifested and efforts are made to treat or reduce complications of the disease (tertiary prevention). However, health care may also actively seek to identify specific asymptomatic diseases or pre-disease conditions in the population by initiating contact and inviting apparently healthy individuals to surveillance and medical screening programs (secondary prevention). In addition to that, efforts should be made to prevent disease and accidents from occurring at all (primary prevention). Although there is no agreed-upon definition of what a medical screening is, most definitions reflect a procedure where health care offers apparently healthy individuals the opportunity to undergo a test to identify those who are at high risk of suffering from a disease or a pre-disease condition, and thereafter offers them further investigations and treatment (2-5) (Figure 1). A medical screening can either address a group of individuals in the general population who are thought to be at risk in so-called mass screening or population-based screening (e.g. mammography screening for breast cancer of women in certain age groups), or it can address targeted risk groups in so-called risk-group screening or selective screening (e.g. colonoscopy screening of persons carrying...
mutations associated with hereditary colon cancer). If individuals seek health care for a specific symptom and in conjunction with that are offered tests for other conditions, this is defined as opportunistic screening. This should not be confused with the concept of active case-finding, which is another method for early detection of disease, although it differs from screening in the sense that it is preceded by an indication that the individual may suffer from the particular disease in focus. However, active case-finding and risk-group screening are concepts that are used interchangeably in the literature. Regular examinations, like those currently being offered within the child welfare surveillance program, may also be considered as a type of screening, although they are customarily referred to as surveillance. The common basis for all of the above-mentioned methods is the idea that early recognition of a disease or pre-disease condition is better than finding it at a later (and possibly more advanced) stage.

Figure 1. Illustration of the concept of mass screening. Apparently healthy individuals are offered a screening test (the net) that sieves out those at risk of or already affected by a disease (figures in red) from the healthy ones (figures in green). Those who are sieved out are then offered further tests to confirm or exclude the diagnosis.
Even if incentives for implementing a mass screening can be seen as efforts made primarily for individual health gains, society may also benefit from finding a disease early. In fact, some of the first screening programs aimed at controlling endemic communicable diseases and from a health-economic perspective in terms of resources saved, early detection of disease may be beneficial for society through productivity gains and reduced treatment costs (2).

The idea behind early detection of a disease through health surveillance or screening programs is attractive: early detection of a pathological process that has already started, but is detected at a time when the condition is reversible, offers better options for treatment and also reduces the risk for further complications. However, programs for early detection of disease that target apparently healthy people also raise specific ethical concerns (6). Individuals invited to a screening should be provided with enough information to make an informed decision as to whether or not to take part. These prerequisites are of even greater importance when the target population comprises children or adolescents not entitled to decide by themselves whether or not to participate. Further, the potential harms and benefits, as well as economic, practical and medical dilemmas, should be thoroughly scrutinized before any implementation of a screening program (6-8). As a guide in selecting conditions that would be suitable for mass screening, certain screening criteria have been set up. The first criteria were written by Wilson and Jungner in a report from the World Health Organization (WHO) (3) (Table 1). Although other sets of modified criteria have been proposed, the majority overlap with the classic criteria (4). These criteria will be discussed later in this thesis.

Table 1. The classic screening criteria of Wilson and Jungner (3).

<table>
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<td>1. The condition sought should be an important health problem.</td>
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<td>2. There should be an accepted treatment for patients with recognized disease.</td>
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<td>3. Facilities for diagnosis and treatment should be available.</td>
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<td>4. There should be a recognizable latent or early symptomatic stage.</td>
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<td>5. There should be a suitable screening test or examination.</td>
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<td>6. The screening test should be acceptable to the population.</td>
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<td>7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
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<td>8. There should be an agreed policy on whom to treat as patients.</td>
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<td>9. The cost of finding the cases (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.</td>
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<td>10. Case-finding should be a continuing process and not a “once and for all” project.</td>
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What screening tests are offered to Swedes today?
There are some minor regional variations on screening tests offered within Sweden, since national guidelines for most screening programs are lacking and implementation of screening programs are decided upon on a regional political level. In general, the following tests are offered to all Swedes in the targeted population.

Even before we are born, we (or rather our mothers) are offered screening tests for various conditions within the frame of antenatal care. In Sweden and most other European countries, pregnant women are offered tests for syphilis, hepatitis B, HIV, rubella immunity and anemia. Antenatal care also offers ultrasound examination for determination of gestational age and number of fetuses as well as a method for screening for malformations. After birth all infants are offered a physical examination with screening for various conditions (e.g. congenital heart disease, malformations, cataract, cryptorchidism, and congenital hip dislocation). In addition, a screening test for hearing loss using otoacoustic emission technology is conducted (9). At the age of 48 hours all infants are offered a screening test with blood sample analysis for 24 rare, severe, but treatable, metabolic diseases (10).

Throughout childhood we are continuously offered screening aimed at early detection of abnormalities to give options for treatment and early intervention. In the child welfare program offered to all children in Sweden, among others, weight and height are measured to detect impaired growth and parents are interviewed to determine if the child has any developmental or psychiatric problems (9).

The medical screening offered to adults by health care is not as frequent as during childhood. Women aged 23-60 years are offered an examination for early detection of precancerous lesions or cancer of the uterine cervix, and women aged 40-74 years are offered mammography screening for early detection of breast cancer (11). Screening programs for abdominal aortic aneurysm are currently offered to men at the age of 65 years in some county councils, although the benefits and drawbacks of this screening are the subject of continuous debate (12-15). This is also the case for prostate cancer screening, concerning which a lively debate has been ongoing for over a decade, even though it has not yet been implemented. Many other screening programs have also been suggested to be implemented, among them mass screening for celiac disease.
Celiac disease
Celiac disease (CD) is a chronic immune-mediated systemic disease, triggered by ingestion of dietary gluten in genetically predisposed individuals (16). The disease may have its onset at any time during the life span (17), with a variable combination of gluten-dependent signs and symptoms (18). CD is characterized by small intestinal inflammation and villous atrophy, and the presence of CD serological markers and small intestinal enteropathy are used in the diagnostic work-up confirming the diagnosis (16, 19).

Increasing occurrence of celiac disease
Over past decades CD occurrence in children has emerged from being considered a rare disease to being perceived as a public health problem. In one of the earliest studies, based on individuals applying for priority food rations in the U.K. during the Second World War, the incidence rate of CD was 1 per 135 000 person-years among children below 15 years of age (20). During subsequent decades the reports of increased CD occurrence in Ireland (21), Scotland (22) and Switzerland (23) may have partly reflected an increased detection rate facilitated by increased awareness, and later by the development of more accessible diagnostic tools. The subsequent development of serological markers indicative of CD made it possible to perform population-based prevalence studies estimating not only the presence of those who were being clinically detected, but also the presence of subclinical or asymptomatic CD cases. With large geographical differences, such population-based screening studies have shown a total biopsy-proven CD prevalence in the general child population ranging from 0.3-3%, always with the majority of cases being previously undiagnosed (24-27). Even if CD has mostly been reported in populations in Europe and North America, the presence of the disease in other parts of the world is now increasingly being reported (28-31). Furthermore, a “true” increase in CD occurrence, in terms of increased prevalence when comparing results from population-based screening studies at different time periods, has been seen in Sweden (24, 32), Finland (33) Denmark (34) and the U.S. (17).

Etiology
CD develops in interplay between necessary environmental and genetic factors (18). Ingestion of gluten found in wheat, rye and barley is a prerequisite for disease development (35). CD is strongly associated with the alleles encoding for alfa- and beta subunits of the
human leukocyte antigen (HLA) heterodimers HLA-DQ2 and DQ8. The non-HLA alleles identified as being associated with the disease seem to make only a modest contribution to disease development (35). Environmental and life-style factors (also besides gluten) are likely to play a role in CD development, which became obvious by the Swedish CD epidemic (36). In the mid 1980’s the incidence of CD in children below two years of age within a few years increased to levels higher than ever previously reported, and after a ten-year period returned to the previous level. Later results from an incident case-referent study, combined with an ecological analysis, suggested that half of the epidemic was a consequence of changes over time in infant feeding (36, 37). Breast-feeding reduced the risk for CD (37, 38), especially when still on-going while gluten was gradually introduced into the infant’s diet (37). The search for other contributing environmental- and life-style factors is on-going (39).

Clinical presentation
CD may present at any age, and with a large variety of signs and symptom including tiredness, abdominal distension, anorexia, diarrhea, vomiting, and anemia (17, 40-42). The clinical presentation in children has changed over time, with increased age at diagnosis and a decreased proportion of children presenting with gastrointestinal symptoms alone today (43). Clinically detected CD cases may still present with gastrointestinal problems, especially in younger children, but the disease is nowadays increasingly being diagnosed in patients with extra-gastrointestinal symptoms or in asymptomatic children detected by risk-group screening because of having a CD-associated condition (42, 43).

Diagnostics
Recent guidelines posed by the European Society of Pediatric Gastroenterology and Hepatology Association (ESPGHAN) suggest that the CD diagnosis should be based on analysis of CD serological markers, HLA-DQ2 and HLA-DQ8 genotyping, an initial biopsy from the small intestine and a clinical and serological follow-up (16).

Serological markers
Serological markers indicative of CD have been available since the beginning of 1980s and the diagnostic accuracy has gradually improved with the increasing quality of available commercial kits. The ELISA-based analysis of immunoglobulin A-antibodies directed against the CD autoantigen tissue-transglutaminase (tTG-IgA) is most commonly used today. Studies on the pediatric population have
shown that high tTG-IgA levels are highly suggestive of CD and the marker has a good overall diagnostic accuracy in the clinical setting (44, 45). Tests based on endomysial antibodies (EMA) have the drawback that the analytical procedure is user-dependent and expensive, but show excellent diagnostic accuracy (45, 46), while tests based on deamidated gliadin peptide (DGP) antibodies show inferior diagnostic accuracy compared to tTG-IgA (47). Individuals with selective IgA-deficiency have an increased risk of developing CD. Therefore, it has been suggested that the total level of serum IgA (s-IgA) should always be analyzed when investigating a patient on suspicion of CD, and if low values of s-IgA are found, tests based on IgG antibodies should be evaluated (16).

**Genetic markers**
Tests for detection of the alleles encoding for HLA-DQ2 and HLA-DQ8 are now available in clinical practice and have become less expensive lately, as the methods have developed (48). HLA-DQ2 and HLA-DQ8 testing has a high negative predictive value and is therefore a useful tool for excluding the diagnosis (16). It has been suggested that non-HLA genetic variants, identified as being associated with CD in recent genome-wide association studies, should be included in the risk prediction for CD as a complement to testing for the alleles encoding for HLA-DQ2 and HLA-DQ8 (49). However, such genetic risk prediction is not (yet) included in clinical practice.

**Small intestinal biopsy**
Demonstration of enteropathy in the small intestine is the gold standard for CD diagnosis, although recent guidelines suggest that the biopsy may not be needed if the patient has very high values of serological markers (>ten times the upper limit of normal), together with presence of HLA-DQ2 or HLA-DQ8 and a clinical and serological response to the gluten-free diet (16). The different grades of inflammation and villous atrophy in the mucosa of the small intestine may be classified according to the Marsh-Oberhuber criteria: 0=normal, I= intraepithelial lymphocytosis (IEL) (>30 IEL/100 enterocytes), II= intraepithelial lymphocytosis and crypt hyperplasia, IIIa=partial villous atrophy, IIIb=subtotal villous atrophy, and IIIc=total villous atrophy (50).

**Treatment**
The only available treatment, a strict gluten-free diet, i.e. exclusion of all foods containing wheat, rye or barley, is an effective treatment that
restores the intestinal mucosa and resolves symptoms in those with symptomatic CD (18, 51-53). However, adhering to a gluten-free diet may result in inadequate dietary intake regarding quality of macronutrients and quantity of minerals and vitamins (54).

**Treatment’s impact on quality of life**

Quality of life, and more specifically health-related quality of life, refers to “the physical, psychological and social domains of health, seen as distinct areas that are influenced by a person’s experiences, beliefs, expectations and perceptions” (55). Quality of life and health-related quality of life are often measured with generic or disease-specific quantitative instruments in order to evaluate human and financial costs of healthcare interventions and to understand the burden of disease (55).

Being diagnosed with CD, and adhering to lifelong dietary restrictions, poses challenges in daily life (56-58). Most studies evaluating how the CD diagnosis and treatment impacts quality of life have used quantitative instruments and involved adult patients (51, 59-67). In some of these studies the effect of gluten-withdrawal on quality of life seems to be related to amount of health problems at diagnosis (59, 61, 62). In general, treated adult CD patients rate similar quality of life as the general population (59, 62-65). Interestingly a few studies have shown that women with CD rate their quality of life lower to their healthy female controls, whereas men with CD rate their quality of life similar to their male controls (65, 66), and a difference in quality of life when comparing women and men with CD has also been demonstrated (63, 67). Qualitative studies have explored that the difference in how women and men with CD are rating their quality of life seems to be impacted by gender-related coping strategies (68).

With a few exceptions, previous studies on the impact of treatment on quality of life in CD children or adolescents have also employed quantitative methods (69-75). One study showed lower quality of life in CD children than in the healthy reference group, but the CD children scored higher quality of life than children with asthma, rheumatoid arthritis and diabetes (69). In another study, noncompliant CD children experienced lower quality of life compared to compliant CD children, who actually rated their quality of life similar as healthy peers (73). Treated CD children with quality of life similar to that of the reference population have been described also by others (70, 72). A qualitative study on CD adolescents explored daily life difficulties of
living with CD and found that adhering to the diet may even produce stigma experiences (76).

**Associated conditions**
CD is more prevalent among patients with unexplained iron deficiency anemia, or with certain chromosomal aberrations such as Turner's syndrome and Down syndrome (18). CD also appears to be overrepresented in patients with IgA-deficiency (77). The association between CD and other autoimmune diseases is well-established with an increased prevalence of CD in patients with for example type 1 diabetes, autoimmune thyroid disease or juvenile chronic arthritis (16, 53). Whether the association between CD and other autoimmune diseases is related to untreated disease with persistent small intestinal enteropathy, or shared etiological factors, is largely unknown. Family members of individuals with CD are also at increased risk of developing the disease (78), due to shared genetic predisposition.
Has the time come for mass screening for celiac disease?

Although recognition of CD within clinical practice has increased over time (79), most CD cases still remain undiagnosed (24, 80, 81). Thus, current guidelines (16) focusing on active case-finding and testing risk groups within clinical practice do not identify the majority of cases. Intensified efforts to find undiagnosed cases are suggested, and have resulted in an intense debate concerning whether or not to implement a general CD mass screening (82-92). The classical screening criteria of Wilson and Jungner (Table 1) are partly fulfilled, but mass screening for CD is nevertheless controversial. Factors that need further exploration include the natural history of screening-detected CD and the cost-effectiveness of a CD mass screening. Also, suitable strategies for finding CD in a mass screening, as well as studies on the consequences of finding the disease for those being diagnosed, are still lacking.

Finding celiac disease in a mass screening

If a mass screening is implemented, serological and genetic CD-markers would play roles as screening-tools for CD, but a confirmatory small intestinal biopsy revealing mucosal damage will most likely still be considered as the gold standard method for verifying a screening-detected CD diagnosis. However, even if serological CD-markers with excellent diagnostic accuracy within the clinical setting are available, it is not well studied how they work in a mass-screening situation, i.e. when targeting the general population. In addition, the possible role for detection of alleles encoding for HLA-DQ2 or HLA-DQ8 in a mass screening strategy needs to be evaluated. Factors to consider include the proportion of CD cases identified, the number of unnecessary biopsies performed, as well as costs and ethical dilemmas involved in performing genetic testing and storing the results.

Methods for selecting those needing to have a blood sample analyzed for CD-markers would be useful in a mass-screening situation. If a simple tool like a questionnaire could be used to identify those with a higher risk of CD, resources would be saved and fewer persons would need to undergo blood sampling (and await the results). In fact, a questionnaire-based case-finding approach for selecting persons for blood sampling has previously been explored, but the diagnostic accuracy of such a screening tool remains unknown due to the lack of a control group (93). Also, whether
children or their parents should be addressed in such an attempt needs further exploration.

**Consequences of being found in a mass screening**

Before implementation of CD mass-screening programs, their acceptability to the population concerned should be addressed. In a study of children involved in a CD screening, but before knowledge of their CD status, the blood sampling for serological markers seemed fairly acceptable, and although some children experienced anxiety, they had or were provided with tools allowing them to cope well and gain confidence (94). However, the acceptability of the diagnosis and treatment following a positive result should also be addressed. No previous study has explored the experiences of children or adolescents who actually receive a CD diagnosis through mass screening. Understanding their perspective will help in identifying difficulties associated with this experience and in guiding healthcare providers in their management of these patients. The effect of a screening-detected CD diagnosis on quality of life has received relatively little study, especially in children and adolescents (95). A Dutch follow-up study conducted on screening-detected CD children reported that 10 years after diagnosis the majority of cases (81%) followed a gluten-free diet with beneficial effects on symptoms (70). They also reported a health-related quality of life equal to that of the general population (70). Nevertheless, even if a gluten-free diet has been reported to have beneficial effects for screening-detected CD children (70, 96), it involves some social dilemmas (58, 76), and the motivation and the benefits of complying with the diet among screening-detected CD cases have been questioned (85). In contrast to the Dutch study mentioned above, compliance with the gluten-free diet that was low as 32% was reported among screening-detected Italian adolescents (97), whereas strict adherence to the gluten-free diet has varied between 40% and 91% in different studies of screening-detected CD adults (61, 98, 99).

In summary, before implementing any future mass screening for CD there are some areas that need further exploration. Studies to establish a suitable strategy for finding undiagnosed CD in the general population are essential. In addition, studies exploring how a screening-detected CD diagnosis impacts quality of life, especially when diagnosed during childhood and adolescence, are warranted (85, 91). Further, it is also important to explore factors that motivate compliance with the treatment and how the treatment impacts on symptoms among screening-detected children and adolescents.
Aims
The overall aim of this thesis is to evaluate different strategies for finding 12-year-olds with undiagnosed CD in the general population and to explore experiences of those receiving a CD diagnosis in a mass screening.

Specific aims:

I. To evaluate strategies for finding undiagnosed CD in a general population of 12-year-olds (Paper 1, Paper 2).

II. To explore adolescents’ and parents’ experiences of having the adolescent’s CD detected through mass screening, as well as their attitudes towards future mass screening (Paper 3, Paper 4).

III. To compare adolescents’ and parents’ recognition of symptoms before diagnosis, as well as treatment compliance and changes in perceived health after diagnosis. (Thesis).
Material and methods

Study context
This thesis emanates from the two-phased Swedish multicenter CD screening study called ETICS - Exploring the Iceberg of Celiacs in Sweden (100). The ETICS-study was designed by a group of pediatricians from the different study sites and further developed by a multidisciplinary research group also including dieticians, social workers, health economists, epidemiologists, geneticists, and PhD students. With the Swedish epidemic of CD (36) as the starting point, the ETICS-study aimed at comparing the total CD prevalence in two different birth cohorts (born during and after the epidemic, respectively). The ultimate aim was to explore options for primary prevention. This large-scale screening study also provided suitable options for obtaining increased knowledge concerning another important research topic within the CD field, namely evaluation of CD mass screening with respect to consequences both for the individual and for society. The screening approached children born in 1993 and 1997 when they reached 12 years of age (in 2005-2006 and 2009-2010, respectively). It was conducted in five study sites across Sweden: Lund, Växjö, Norrtälje, Norrköping, and Umeå (Figure 2). Each site included schools in the city itself as well as the surrounding countryside. This thesis is based on data from the first field phase of the ETICS-study.

Figure 2. Study sites across Sweden for the ETICS-study.
The screening

At school, all sixth-graders in the participating schools received an invitation letter to the screening. The invitation letter contained information about the aim of the study and the screening procedure, with one section specifically addressing the parents, and another the children. The letter also included information on possible advantages and disadvantages of participating in the study, as well as a fact-sheet on CD.

After obtaining written informed consent from their parents, blood samples from all participating children were collected at school by the research nurses and/or school nurses. Local anesthetic cream was applied before the blood was drawn, and afterwards the children were given a piece of fruit, something to drink, a cookie and a yo-yo.

The serum samples were analyzed at a centralized laboratory and if the test results for the CD serological markers indicated suspicion of CD, the parent/s received a telephone call from a pediatrician at the study site. The parent/s was informed by telephone about the test results and the child and parent/s were offered an appointment at the closest pediatric clinic.
At this visit further information about CD was given and the child was recommended to undergo a small intestinal biopsy. Those who accepted received a time for a new policlinic visit for the small intestinal biopsy. The biopsy samples were taken, under sedation, either by endoscope or by suction capsule using a Storz or Watson capsule.

All children who underwent a small intestinal biopsy were offered a visit in order to receive the results. Those with biopsy results confirming a CD diagnosis were recommended to adhere to a lifelong, strict, gluten-free diet. Support was offered including consultation with a dietician and follow-up visits to a pediatrician.
Participants: children or adolescents?
The participants in the ETICS-study are interchangeably referred to as *children* or *adolescents* in this thesis. The decision to use both concepts is based on an effort to refer to the participants correctly in relation to their chronological age and to their development and increasing independence and autonomy. We also wanted to use the correct term as defined by Medical Subject Headings (MeSH), the U.S National Library of Medicine’s controlled thesaurus (101).

At the time of the screening, the participants attended 6th grade and the majority of them were 12 years of age. According to MeSH, a person in the age group between 0-12 years is a *child*. Also, the participants were children in relation to the parents, who were formally those deciding upon participation in the study. Therefore, when referring to this period the participants are called *children* or *12-year-olds*.

During the follow-up study the participants attended 8th grade and the majority of them were 14 years of age. According to MeSH, a person in the age group between 13-18 years is an *adolescent*. The word adolescent comes from the Latin word *adolescere*, meaning "to grow up" and adolescence is viewed as a transitional period between childhood and adulthood aimed at preparation for future adult roles. The adolescence is characterized by rapid physical, psychological, and social developmental changes (102). In the follow-up study it was evident that the participants were at a transition stage of both physical and psychological development, which had possibly also been enhanced by the experience of receiving a life-long chronic disease diagnosis. Therefore it seemed appropriate to use the term *adolescents* when referring to the participants in the follow-up study.
An emergent multi-methodological approach
This thesis is based on a combination of quantitative and qualitative methodologies, where the choice of methods was guided by the specific aims posed (Table 2). For evaluating screening strategies (specific aim I), data from questionnaires, serological marker analyses and detection of alleles encoding for HLA-DQ2 or HLA-DQ8 were analyzed with descriptive and analytical quantitative methodology (Papers 1 and 2). For exploring experiences of having the CD detected in the screening (specific aim II), a qualitative methodological approach using focus groups was initially chosen. This decision was based on the notion that experiences of receiving the CD diagnosis and its effect on adolescents’ quality of life constitute a complex and unexplored area. Through focus group discussions we expected to be able to capture an in-depth understanding of both adolescents’ and parents’ own descriptions of their major concerns and to explore norms and attitudes at the group level (103). However, while performing the preliminary analysis of the focus group discussions, we identified a need to explore individual experiences and attitudes in more detail. We therefore decided to triangulate data-collection methods by also including written narratives and short-answer questions from the questionnaire in the analysis (Papers 3 and 4). This mixed-methodology, including both qualitative and quantitative analyses, allowed for exploring experiences and attitudes related to the screening, as well as mirroring how these experiences and attitudes were represented in the study population. Although not considered a major aim of this thesis, interest in comparing children’s and parents’ responses (specific aim III) developed while analyzing the data from the questionnaires and the qualitative inquiry, and the findings will therefore be presented and discussed within the frame of this thesis.

As described above, the pragmatic approach used in this thesis i.e. to choose the mixture of methods that works best to explore the aims, resulted in an emerging mixed methods research approach to address the specific aims II and III (104, 105). Mixed methods research is nowadays considered as the third research paradigm and defined as “the type of research in which a researcher combines elements of qualitative and quantitative research approaches for the broad purposes of breadth and depth of understanding and corroboration” (106). An overview of the thesis in terms of specific aims, and characteristics of the study designs, data sources, informants, analytical approaches and corresponding papers is presented in Table 2.
Table 2. An overview of the thesis in terms of specific aims, characteristics of the study designs, data sources, informants, analytical approaches and corresponding papers.

<table>
<thead>
<tr>
<th>Specific aims</th>
<th>Study designs</th>
<th>Data sources</th>
<th>Informants</th>
<th>Analytical approach</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate strategies for finding undiagnosed CD in a general population of 12-year-olds.</td>
<td>Quantitative--Cross-sectional</td>
<td>Questionnaires</td>
<td>12-year-olds participating in the CD-screening (n=7054), and their parents (n=6294)</td>
<td>Descriptive and analytical. Diagnostic accuracy, Logistic regression</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Quantitative--Cross-sectional</td>
<td>Blood sample analysis of CD-markers</td>
<td>12-year-olds participating in the CD-screening (n=7208).</td>
<td>Descriptive and analytical. Diagnostic accuracy, ROC-curve</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Quantitative--Nested case-referent</td>
<td>Analysis of HLA-alleles in extracted DNA.</td>
<td>Screening-detected CD cases (n=153) and non-CD children, frequency-matched for sex (n=1167).</td>
<td>Descriptive.</td>
<td>2</td>
</tr>
<tr>
<td>To explore adolescents' and parents' experiences of having the adolescent's CD detected through mass screening, as well as their attitudes towards future mass screening.</td>
<td>Quantitative--Follow-up study</td>
<td>Questionnaires</td>
<td>Parents of screening-detected CD cases (n=105).</td>
<td>Descriptive.</td>
<td>3, 4</td>
</tr>
<tr>
<td></td>
<td>Qualitative--Follow-up study</td>
<td>Focus group discussions</td>
<td>Screening-detected CD cases (n=31), and their parents (n=43).</td>
<td>Descriptive and analytical. Grounded Theory, Qualitative content analysis</td>
<td>3, 4</td>
</tr>
<tr>
<td></td>
<td>Qualitative--Follow-up study</td>
<td>Narratives</td>
<td>Screening-detected CD cases (n=91), and their parents (n=105).</td>
<td>Descriptive and analytical. Grounded Theory, Qualitative content analysis</td>
<td>3, 4</td>
</tr>
<tr>
<td>To compare adolescents' and parents' recognition of symptoms before diagnosis, as well as treatment compliance and changes in perceived health after diagnosis.</td>
<td>Qualitative--Follow-up study</td>
<td>Focus group discussions</td>
<td>Screening-detected CD cases (n=31), and their parents (n=43).</td>
<td>Descriptive and analytical. Qualitative content analysis</td>
<td>3, Thesis</td>
</tr>
<tr>
<td></td>
<td>Qualitative--Follow-up study</td>
<td>Narratives</td>
<td>Screening-detected CD cases (n=91), and their parents (n=105).</td>
<td>Descriptive and analytical. Qualitative content analysis</td>
<td>3, Thesis</td>
</tr>
<tr>
<td></td>
<td>Quantitative--Cross-sectional</td>
<td>Questionnaires</td>
<td>Screening-detected CD cases (n=130), and their parents (n=130).</td>
<td>Descriptive and analytical. Mc Nemar's test, kappa(Κ)-statistics</td>
<td>Thesis</td>
</tr>
<tr>
<td></td>
<td>Quantitative--Follow-up study</td>
<td>Questionnaires</td>
<td>Screening-detected CD cases (n=107), and their parents (n=107).</td>
<td>Descriptive and analytical. Spearman rank correlation coefficient, kappa(Κ)-statistics</td>
<td>Thesis</td>
</tr>
</tbody>
</table>

18
**Finding undiagnosed celiac disease (Papers 1 and 2)**

**Participants**
The study basis for both Papers 1 and 2 constituted the first screening phase of the ETICS-study, to which 10041 children were invited and 7567 consented to participate (Figure 3). Previously diagnosed CD was reported by parents at enrollment and ascertained through medical records (n=66). Blood samples from 7208 children (72%, 3467 girls, 3741 boys) without previously known CD were analyzed for CD serological markers. A total of 192 children (2.7%) were found to have elevated levels of CD-markers, and out of those 145 had their CD confirmed by biopsy during the first year of the study (24). During the process of re-evaluating and re-biopsying those with suspected CD, another 8 children received the diagnosis (107). Thus, out of 184 children who were biopsied, 153 (82 girls, 71 boys) finally received a CD diagnosis.

**Figure 3.** Flowchart showing the number of children in the different steps of the screening. (*) indicates the recruitment basis for Paper 1 and (**) indicates the recruitment basis for Paper 2.
Inclusion criteria for Paper 1 were i) having a blood sample analyzed for CD-markers, and ii) having returned questionnaire(s) before knowledge of the results for the CD-markers and either iiiia) fulfilling CD-diagnosis criteria (screening-detected CD) or iiiib) having CD-marker levels below criteria for recommending a biopsy (non-CD children).

Inclusion criteria for Paper 2 were having had a blood sample analyzed for CD-markers. In addition, HLA-DQ2 and HLA-DQ8-analyses were performed in a nested case-referent study in which all screening-detected cases (n=153) and a random selection of non-CD children (n=1167), matched for sex at the group level, were included.

Data sources

Questionnaire addressed to the child
Within two weeks after the blood sampling, but before knowledge of CD status, the children completed questionnaires in the classroom, supervised by the teacher or the site research nurse. To facilitate confidentiality the children’s desks were moved apart so that they were not sitting next to one another. The questionnaire addressed, among other things, information usually asked for in the medical history of children seeking health care for suspected CD. The questionnaire therefore included a section on symptoms, covering items on tiredness, poor appetite, nausea, stomach ache, upset stomach, abdominal gas, bloating, hard stool, loose stool, and lactose intolerance. Response alternatives were never, seldom, sometimes, often, and always over the last six months.
Questionnaire addressed to parents
The parental questionnaires, along with a pre-addressed postage-paid envelope, were brought home from school by the children. Among other things, parents were asked to report the presence of a selection of disorders in the child: anemia, type 1 diabetes, thyroid disease, rheumatic disease, inflammatory bowel disease, vitiligo, alopecia areata, dermatitis herpetiformis, Trisomi 21, and Turner’s syndrome, as well as a family history of CD among first-degree relatives. In addition, parents were also asked to rate the presence of symptoms in the child. For the parental questionnaire there were two postal reminders and one telephone reminder.

Serological markers
All serum samples from children without previously known CD were analyzed for tTG-IgA and for total s-IgA. The analysis of tTG-IgA was performed by enzyme-linked immunosorbent assay (Celikey, Phadia, Freiburg, Germany) in accordance with the manufacturer’s directions. The serum samples were diluted 1:101, and the antibody levels, expressed as arbitrary units per milliliter (U/ml), were calculated from a six-point calibrator curve. The analyses were performed in duplicate and the mean value was subsequently used. Total s-IgA was analyzed using a routine nephelometric method according to the manufacturer’s directions (BN Pro Spec System, Dade Behring, Marburg GmbH, Germany).

In children with intermediate levels of tTG-IgA, additional analysis of EMA-IgA was performed with indirect immunofluorescence technique
using tissue sections from marmoset monkey esophagus mounted on
glass slides (The Binding Site, Birmingham, UK). Analyses were done
according to the manufacturer’s directions. Sera yielding fluorescent
binding to the endomysial structure in a dilution of 1:5 were regarded
as positive and were further diluted to determine the final titer for
which fluorescence was detected. Samples with s-IgA < 0.5 g/L were
also analyzed for tTG-IgG, and if the values were borderline, also for
EMA-IgG.

Serological criteria for recommending a small intestinal biopsy were:
tTG-IgA levels >4 U/mL, tTG-IgG levels >6 U/mL, or intermediate
levels of tTG-IgA (2-4 U/mL) or tTG-IgG (3-6 U/mL), in combination
with EMA positivity (≥1:5).

Genetic markers
In the nested case-referent study, DNA available from children with
screening-detected CD and a random selection of the non-CD
children was analyzed for detection of alleles encoding for the human
leukocyte antigen (HLA) class II DQ-subunits. DNA was extracted
from whole blood in EDTA tubes using QIAamp DNA Blood Maxi
KitDNA or, on a few occasions, from whole blood on filter paper using
the Qiagen Microkit. The alleles were detected using a EU-DQ-test
(Eurospital SpA, Trieste, Italy) according to the manufacturer’s
instructions. The combination of alleles detected refers to different
HLA-DQ-haplotypes (Table 3).

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>x</td>
<td>x</td>
<td></td>
<td>HLA-DQ2</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td></td>
<td>HLA-DQ2</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td></td>
<td>HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td></td>
<td>HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td>HLA-DQ2/HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
<td>x</td>
<td>HLA-DQ2/HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td></td>
<td></td>
<td>non HLA-DQ2/non HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td></td>
<td></td>
<td>non HLA-DQ2/non HLA-DQ8</td>
</tr>
<tr>
<td>x</td>
<td></td>
<td></td>
<td>non HLA-DQ2/non HLA-DQ8</td>
</tr>
</tbody>
</table>

Table 3. Alleles detected by the EU-DQ-test and corresponding HLA-DQ haplotypes
Case ascertainment
At the pathology department at each study site the biopsy samples were stained with hematoxylin and eosin and evaluated according to the Marsh-Oberhuber classification. After the initial diagnostic procedures, following normal clinical routine at the pediatric clinic of the study site, a centralized evaluation was conducted. Following a standardized protocol, an expert pathologist reevaluated all the samples without knowing the results of the local pathologists’ assessments. If there were diagnostic divergences between the local pathologist and the expert pathologist, samples were further evaluated by a second expert pathologist, and diagnostic consensus was reached (107). Criteria for a screening-detected CD diagnosis were i) villous atrophy (Marsh IIIa-IIIc), ii) crypt hyperplasia (Marsh II), or iii) increased count of intraepithelial lymphocytes (Marsh I) in combination with presence of HLA-DQ2/DQ8 haplotype, signs or symptoms suggestive of CD and a clinical or serological response to a gluten-free diet.

Analytical approach
Pearson’s chi-squared test or Fisher’s exact test were used when comparing proportions between two independent groups, e.g. participants versus non-participants. If not normally distributed, such as the ordinal variables capturing response alternatives for symptoms, differences in median values between groups were compared with the Mann-Whitney U-test. Throughout the thesis statistical significance was defined as a two-tailed p-value<0.05. Microsoft Access (Microsoft, Redmond, WA) was used for data handling. For the quantitative analyses the software package PASW Statistic version 17-18 (SPSS Inc., Chicago, IL) and Excel 2011 (Microsoft. Redmond, WA) was used.

Logistic regression
Logistic regression analysis was used to calculate odds ratios i.e. the ratio between the odds of having undiagnosed CD and the odds of not having CD if having a certain CD-associated symptom or condition. As frequency of symptoms among girls at the group level significantly differed when compared with the frequency of symptoms among boys, and as it is well known that a higher proportion of girls have CD diagnosed compared to boys, sex was entered in the model as a potential confounder. Thus, the calculated odds ratios of having unrecognized CD obtained in the analysis were adjusted for sex. Throughout this thesis, statistical significance is defined as an odds ratio with a confidence interval (CI) not including 1.
Accuracy of diagnostic procedures
In this thesis the diagnostic accuracy of different screening strategies for finding undiagnosed CD was calculated. The strategies’ ability to detect CD in those who actually have the disease (sensitivity) as well as the strategies’ ability to identify those who do not have the disease (specificity) were estimated. In addition, we have calculated the probability of having undiagnosed CD in a subject with a positive result (positive predictive value, PPV) as well as the probability of not having undiagnosed CD in a subject with a negative result (negative predictive value, NPV). A schematic overview of how these measures of diagnostic accuracy were calculated is depicted in Figure 4.

<table>
<thead>
<tr>
<th>Screening-strategy</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a true positive</td>
<td>b false positive</td>
</tr>
<tr>
<td>-</td>
<td>c false negative</td>
<td>d true negative</td>
</tr>
</tbody>
</table>

Sensitivity = a/(a+c) Specificity = d/(b+d)

Figure 4. Schematic overview of how the sensitivity, specificity, and positive and negative predictive values were calculated.
Experiences of receiving the diagnosis (Papers 3 and 4)

Participants
All screening-detected adolescents (n=145) who had their CD diagnosed at least a year earlier, and their parents, constituted the recruitment basis for this study. As shown in Table 4, 31 adolescents and 43 parents participated in focus group discussions. The main reason given for non-participation was lack of time, but a few adolescents also expressed reluctance to talk about their disease. However, some parents of adolescents in this latter group did participate. Out of 145 invited to do so, 91 adolescents and 105 parents submitted a written narrative, and 114 parents filled in questionnaires. Information in the qualitative follow-up study was obtained from 117 (81%) of the adolescents, either from the adolescents themselves (n=101) and/or from their parent/s (n=125). These parents represented families of 111 adolescents, i.e. from some families both parents participated. The median age of the adolescents who contributed with written narratives was 14.6 years (range 13.9-15.4) and the median time since diagnosis was 15.9 months (range 11.1-23.2). There were no statistically significant differences in the proportions of girls/boys, the levels of mucosal damage of participating and non-participating adolescents or the educational level of participating and non-participating parents (Pearson’s chi-squared test, p>0.05).
Table 4. Number of invited and participating informants across study sites (papers 3 and 4).

<table>
<thead>
<tr>
<th>Study site</th>
<th>CD-cases</th>
<th>Focus group discussion</th>
<th>Written narrative</th>
<th>Follow-up questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invited</td>
<td>Participated</td>
<td>Invited</td>
<td>Participated</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Adolescents</td>
<td>Parents</td>
<td>n</td>
</tr>
<tr>
<td>Umeå</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Norrtälje</td>
<td>18</td>
<td>18</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Norrköping</td>
<td>17</td>
<td>17</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Lund</td>
<td>65</td>
<td>65</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Växjö</td>
<td>29</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>116</td>
<td>31</td>
<td>43</td>
</tr>
</tbody>
</table>

% females 52 | 54 | 45 | 60  | 52 | 53 | 85  | 52 | 53 | 84  
% of invited -- | 21 | -- | 63  | 72

---

*a All screening-detected CD-cases, with CD diagnosed at least a year ago, formed the recruitment basis

*b Adolescents and their parents were invited

*c In paper 3, only responses from those also participating with narratives were included.

*d Not possible to calculate since we do not know the total number of parents living with the adolescents
Data sources

Focus group discussions
The focus group method was employed for exploring the participants’ experiences, opinions, wishes and concerns related to their participation in the CD screening. The focus group method builds on group interaction and is particularly useful for allowing participants to generate their own concepts on their own terms with their own vocabulary (108). It is widely used in health care research and has been suggested as especially suitable when attempting to elicit children’s or adolescents’ views, since it decreases the power relation between the researcher and the informants (109, 110).

The sampling was purposive with the aim of reaching maximum variation in relation to some specific criteria (103). We wanted to assure that girls and boys, as well as mothers and fathers, were represented in the groups and that we had informants from several study sites. The invitations to the focus groups, one for the adolescents and another for the parents, were sent to their homes, with information about the purpose of the study and that we would contact them shortly. A few replied immediately to confirm their participation, while the others were recruited by a phone call from the research team.
The focus group discussions were held outside the hospital environment, most often in conference centers easily accessible for the participants. Adolescents and parents attended separate groups but were mixed in terms of gender. The author of this thesis moderated most discussions. Two other members of the research team (a pediatrician and a social worker) also participated in some of the discussions. None of these researchers had a professional relationship with the informants.

When introducing the focus groups we emphasized that all opinions were welcomed and that the informants were "the real" experts. The informants were also encouraged to discuss the issues of greatest importance to them to increase the likelihood that their own accounts would take priority. A thematic guide with topics to discuss, vignettes describing situations and dilemmas for adolescents with CD, as well as drawings illustrating various aspects of the CD screening and life thereafter, had been prepared to stimulate the discussions. Both adolescents and parents were encouraged to share experiences of the adolescents’ symptoms and wellbeing before and after treatment, and how the treatment could affect daily life. Reflections on their awareness of CD prior to screening, their reasons for deciding to participate, their experiences of receiving a CD diagnosis through
mass screening and their opinions about mass screening as a general solution were also elaborated on. Reflective notes were continuously taken to guide the subsequent group discussions, indicating that the thematic guide was flexible and developed throughout the data-collection period.

The size of the focus groups ranged from 3 to 8 participants. The interviews lasted 60 to 90 minutes and were all digitally recorded. Data collection continued until saturation was obtained. The recorded files were transcribed verbatim by an assistant, and later crosschecked by the author of this thesis to ensure accuracy. Transcribed texts were entered into the software Open Code (111).

Follow-up questionnaires with written narratives

Along with answering separate follow-up questionnaires, both the adolescents and their parents were invited to write short narratives. In the instructions for the narratives they were encouraged to share their personal experiences of the adolescent’s CD diagnosis, and specifically to elaborate on how they felt when receiving the diagnosis, any change in perceived health or other daily life consequences, and their recommendations about possible future CD screening. The length of the narratives ranged from one to two handwritten pages and all were transcribed verbatim.
In addition, the follow-up questionnaires for both the adolescents and their parents included two multiple choice questions concerning: i) compliance with the gluten-free diet with response alternatives always, often, sometimes, and never, and ii) perceived wellbeing today compared to before the CD diagnosis with response alternatives much better, somewhat better, no difference, somewhat worse, and much worse.

The parental questionnaire also included two questions regarding future screening: i) whether a CD screening should be implemented, with pre-determined response alternatives (yes, no, don’t know); and ii) at what age a screening should preferably be conducted (they were asked for a suggestion). To secure confidentiality between adolescents and parents, they were instructed to return the questionnaires in separate envelopes.
Qualitative analytical approach
The primary steps of the analysis were based on a Grounded Theory framework (112), which was chosen because of its systematic approach to new and unexplored topics, such as how a screening-detected CD diagnosis may be experienced by the affected adolescents and their parents. Although the qualitative follow-up study was initially planned with the aim of exploring symptoms prior to diagnosis and changes in perceived health after diagnosis and initiated treatment, it became evident from the first focus group discussions that issues other than changes in health were of importance to the adolescents and their parents. Therefore, in line with the emergent design of a Grounded Theory study, the topic guide for the focus group discussions developed throughout the process. As mentioned earlier, we identified a need for a data collection method that also explored individual experiences and perceptions in more detail, in addition to being able to explore the representativeness of the findings from the focus groups. We therefore complemented the data collection with written narratives and data from short-answer questionnaires.

The focus group discussions and written narratives from both the adolescents and their parents were jointly analyzed. First, all texts from transcribed focus group discussions and written narratives were read through to gain a flexible frame of reference. Thereafter the text was entered into the Open Code software program and subjected to an open coding process. In the open coding process each line, or sentence, was labeled with one or more codes to conceptualize the meaning of the text. Most of the codes were kept close to the original data to ensure that the interpretation was grounded in data, which also implied a low grade of abstraction at this stage of the analysis.

To facilitate further analysis the author of this thesis used a prefix before the actual code, e.g. codes reflecting concepts related to how the child felt before diagnosis and treatment were labeled with the prefix “before treatment”. After labeling the whole text with open codes the original text was left in order to reach a higher level of interpretation and abstraction. All open codes were exported to a Word document and subjected to a sorting procedure in which codes belonging to a shared concept, i.e. a content area (in time or in place) were clustered. Hence, at this stage the analysis rather followed the steps of Qualitative content analysis, as described by Graneheim and Lundman (113). The prefixes of the open codes facilitated the sorting procedure.
After identifying the content areas, the codes within each content area were compared. An oscillation process, moving between open codes and the original text, was the basis for comparing and interpreting the underlying meaning of the participants’ experiences. Codes sharing communalities were grouped into sub-categories. These sub-categories were examined for links between them and later formed categories. Throughout this process, sub-categories and categories were continuously compared with the original text to ensure that the results were well grounded in the data.

After performing the above-mentioned steps of the analysis, it was decided to present the results in two separate papers. Paper 3 is based on a Grounded Theory analysis in order to develop a conceptualized model (but still kept close to the informant’s views) of how a screening-detected diagnosis impacts on adolescents' quality of life. In paper 4 we wanted to focus specifically on the content areas identified during the initial analysis process to capture the lived experiences of and the attitudes towards CD screening, and we therefore employed qualitative content analysis (113). Paper 4 also included a quantification of the categories derived from the qualitative analysis, since narratives were written by a representative sample of the study population. Each individual narrative was reviewed to judge which of the categories within each content area were supported, or not reflected upon. For the purpose of this thesis the results from Papers 3 and 4 will be presented as a synthesis.
Comparing children’s and parents’ responses (Thesis)

Participants
The children later invited to the follow-up study (n=145), and their parents, formed the recruitment basis for these analyses. Questionnaires filled in by both children and their parents before knowledge of CD status were available from 130 (90%) of those families. In total, 91 children and 105 parents contributed written narratives and 31 children and 43 adolescents participated in focus group discussions. In the follow-up study, questionnaires answered by children with corresponding parents were available from 107 families.

Data sources
In the questionnaires (see pages 20-21) filled in separately by children and parents before knowledge of CD status, questions on the presence of seven symptoms in the child were addressed to both the children and their parents. Symptoms asked for were tiredness, nausea, stomach ache, upset stomach, abdominal gas, hard stool and loose stool with response alternatives always, often, sometimes, seldom or never over the last six months.

In the focus groups and in the written narratives (see pages 26-30), information on the child’s symptoms before diagnosis was obtained from both adolescents and parents.

In the follow-up questionnaire (see page 30) the adolescents were asked to answer two multiple choice questions concerning: i) self-reported compliance with the gluten-free diet with response alternatives always, often, sometimes, and never, and ii) perceived wellbeing today compared to before the CD diagnosis with response alternatives much better, somewhat better, no difference, somewhat worse, and much worse. The same questions were posed to the parents and to the adolescents, which made comparison of compliance and change in wellbeing after initiated treatment possible.
Analytical approaches

Qualitative analytical approach
The qualitative analysis of data from focus groups and written narratives was used to explore symptoms prior to diagnosis that were recognized by the adolescents and the parents (see pages 31-32).

McNemar's test
McNemar’s test is a chi-square test for comparing proportions in two dependent or paired groups and was used when comparing proportions of children with symptoms, as reported by the children themselves and as reported by their parents.

Correlation
To assess whether or not there was a significant relationship between adolescent and parent ratings of compliance with the gluten-free diet and change in wellbeing after diagnosis, Spearman’s rank correlation coefficients were calculated.

Kappa (Κ) statistic
The kappa (Κ) statistic was used to measure the agreement between the child’s and the parent’s reporting of the child’s symptoms prior to diagnosis, the perceived change in wellbeing, and compliance with the gluten-free diet (thesis). The following guidelines for interpreting the kappa(Κ)-value have been proposed (Table 5).

Table 5. Guidelines for interpretation of kappa (Κ). Adopted from Byrt et al. (114).

<table>
<thead>
<tr>
<th>Kappa (Κ)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93-1.00</td>
<td>Excellent agreement</td>
</tr>
<tr>
<td>0.81-0.92</td>
<td>Very good agreement</td>
</tr>
<tr>
<td>0.61-0.80</td>
<td>Good agreement</td>
</tr>
<tr>
<td>0.41-0.60</td>
<td>Fair agreement</td>
</tr>
<tr>
<td>0.21-0.40</td>
<td>Slight agreement</td>
</tr>
<tr>
<td>0.01-0.20</td>
<td>Poor agreement</td>
</tr>
<tr>
<td>&lt;=0</td>
<td>No agreement</td>
</tr>
</tbody>
</table>
Ethical considerations
All participation was based on voluntary decisions. Written informed consent was obtained from caregivers of all children participating in the screening. When inviting them to the follow-up study we were aware that receiving the diagnosis may have been difficult for the adolescents, and their parents, and we were prepared to be sensitive to their reactions. During the first focus group sessions we found that a few adolescents had more or less been persuaded to participate by their parents. When inviting adolescents and parents to the following focus groups we therefore specifically also asked to talk on the phone with the adolescents to emphasize that their decision to participate was voluntary and should not be decided upon only by their parents. During the focus group discussions it was also emphasized that the informants should only share things they felt confident in sharing. A pediatrician was present in conjunction with all meetings to allow adolescents and parents to ask questions after the sessions. We believe that asking the adolescents and parents for their opinions also gave a sense of empowerment. The Regional Ethical Review Board in Umeå, Sweden, approved the study [Dnr UmU 04-156M].
Results

Strategies for finding undiagnosed celiac disease

Asking children for CD-associated symptoms (Paper 1)
Before knowing their CD status, children participating in the screening filled in questionnaires regarding CD-associated symptoms. Tiredness was the most common symptom in both CD- and non-CD children. In logistic regression modeling, adjusted for sex, having symptom(s) did not significantly increase the odds of having undiagnosed CD (Table 6).

Table 6. Numbers and proportions of non-CD children and screening-detected CD children reporting symptoms before knowledge of the results of the CD serological markers, with odds ratios and 95% confidence intervals.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Non-CDb n=6905</th>
<th>CD n=149</th>
<th>Odds ratio (CI)d CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%c</td>
<td>n</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1175</td>
<td>17.3</td>
<td>26</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>338</td>
<td>5.1</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>230</td>
<td>3.4</td>
<td>4</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>473</td>
<td>7.1</td>
<td>10</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>353</td>
<td>5.2</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal gas</td>
<td>337</td>
<td>5.0</td>
<td>10</td>
</tr>
<tr>
<td>Bloating</td>
<td>150</td>
<td>2.2</td>
<td>4</td>
</tr>
<tr>
<td>Hard stool</td>
<td>493</td>
<td>7.4</td>
<td>17</td>
</tr>
<tr>
<td>Loose stool</td>
<td>157</td>
<td>2.4</td>
<td>4</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>336</td>
<td>5.0</td>
<td>9</td>
</tr>
<tr>
<td>Any symptome</td>
<td>2283</td>
<td>33.1</td>
<td>50</td>
</tr>
</tbody>
</table>

a Self-reported symptom present often or always during the last six months.
b Children with CD-marker levels below criteria for recommending a biopsy (see method section) were considered as non-CD children.
c Internal non-response ranged for CD-cases from n=1 to n=7, and for non-CD children from n=126 to n=285. Proportions were calculated by using total number of responses for each item as denominator in the different groups. Thus, internal non-responses were excluded for each item.
d Odds ratio of being a screening detected CD case if symptom(s) present compared to if symptom not present with 95% confidence interval (CI), calculated by logistic regression, adjusted for sex.
e Any of the symptoms listed above.
**Questionnaire on symptoms as a screening tool**

If the presence of one or more of the symptoms asked for in the questionnaire were to be used as a screening tool for CD, 50/149 (34%) of the hitherto undetected CD cases in our study population would have been identified (Figure 5). Such a strategy had a sensitivity of 34%, a specificity of 67%, a positive predictive value of 2% and a negative predictive value of 98%. CD prevalence was similar in the groups with and without any symptoms (2.1% vs. 2.1%, Fisher’s exact test, p=0.93).

**Figure 5.** Finding CD by asking for reported CD-associated symptoms* among 7054 children without previously known CD.

*Any of the symptoms [tiredness, poor appetite, nausea, stomach ache, upset stomach, abdominal gas, bloating, lactose intolerance, hard stool, and/or loose stool], often or always during the last six months.
Asking parents for CD-associated conditions (Paper 1)

From logistic regression modeling, adjusted for sex, children with either thyroid disease or Trisomi 21 had significantly increased odds of having screening-detected CD, even if the confidence intervals were broad (Table 7).

Table 7. Numbers and proportions of non-celiac disease (non-CD) children and screening-detected celiac disease (CD) children with CD-associated conditions, reported by their parents before knowledge of results of the CD-serological markers, with odds ratios and 95% confidence intervals.

<table>
<thead>
<tr>
<th>CD-associated condition</th>
<th>Non-CD n=6154</th>
<th>CD n=140</th>
<th>Odds ratio (CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo</td>
<td>83</td>
<td>2</td>
<td>1.4 (0.3-4.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>57</td>
<td>2</td>
<td>0.9 (0.4-6.4)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>17</td>
<td>2</td>
<td>0.3 (1.2-23)*</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>22</td>
<td>1</td>
<td>0.4 (0.3-15)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td>1</td>
<td>0.3 (0.4-21)</td>
</tr>
<tr>
<td>Trisomi 21</td>
<td>4</td>
<td>1</td>
<td>0.1 (1.3-102)*</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>17</td>
<td>0</td>
<td>0.3 (0.3-15)</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>19</td>
<td>0</td>
<td>0.3 (0.3-15)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>5</td>
<td>0</td>
<td>0.1 (0.3-15)</td>
</tr>
<tr>
<td>Turner’s syndrome</td>
<td>2</td>
<td>0</td>
<td>0.1 (0.3-15)</td>
</tr>
<tr>
<td>CD family history b</td>
<td>138</td>
<td>6</td>
<td>2.2 (0.9-4.6)</td>
</tr>
<tr>
<td>Any associated condition c</td>
<td>367</td>
<td>14</td>
<td>6.0 (1.0-3.1)</td>
</tr>
</tbody>
</table>

For condition present compared to if condition not present with 95% confidence interval (CI), calculated by logistic regression, adjusted for sex

b CD reported as present in the child’s biological mother, father and/or siblings.

c Any of the conditions listed above.

Among children with previously diagnosed CD, 41% had any of the CD-associated conditions listed above, compared to 10% among screening-detected cases, and 6% among non-CD children (Pearson’s chi-squared test, p<0.001) (Paper 1). In addition, 21% of the children with previously diagnosed CD had at least one first-degree relative with CD, compared to 4.3% of the screening-detected CD cases and 2% of the non-CD children (Pearson’s chi-squared test, p<0.001) (Paper 1).
**Questionnaire on associated conditions as a screening tool.**
If the presence of one or more of the CD-associated conditions asked for in the parental questionnaire were to be used as a screening tool, 14/140 (10%) of the hitherto undetected CD cases in our study population would have been identified (Figure 6). Such a strategy had a sensitivity of 10%, a specificity of 94%, a positive predictive value of 3.7% and a negative predictive value of 98%. There was no significant difference in CD prevalence between the groups with and without any CD-associated conditions (3.7% vs. 2.1%, Fisher’s exact test, p=0.07).

**Finding undiagnosed CD by asking parents for…**

**Figure 6.** Finding CD by asking parents for CD-associated conditions* in 6294 children without previously known CD.

**Parent reporting that the child suffered from ≥1 CD-associated condition(s) [anemia, type 1 diabetes, rheumatic disease, thyroid disease, inflammatory bowel disease, vitiligo, alopecia areata, dermatitis herpetiformis, trisomi 21, Turner’s syndrome and/or with ≥ 1 first-degree relative(s) with CD].**
Asking children and parents for CD-associated symptoms and conditions (Paper 1)

In summary, Figure 7 shows a hypothetical screening tool for CD comprising a combination of the child questionnaire on symptoms and the parental questionnaire on CD-associated conditions.

As shown, even when using the combined approach only 52 (38%) of the undetected cases would be identified at a cost of blood sampling 2282 (37%) of the children. Sensitivity for this combined case-finding tool was 38%, specificity 63%, positive predictive value 2%, and negative predictive value 98%.

Finding undiagnosed CD by asking children and parents for…

Figure 7. Finding CD by asking children for CD-related symptoms* and parents for CD-associated conditions** in 6226 children without previously known CD.

*Any of the symptoms [tiredness, poor appetite, nausea, stomach ache, upset stomach, abdominal gas, bloating, lactose intolerance, hard stool, and/or loose stool], often or always during the last six months.

**Parent reporting that the child suffered from ≥1 CD-associated condition(s) [anemia, type 1 diabetes, rheumatic disease, thyroid disease, inflammatory bowel disease, vitiligo, alopecia areata, dermatitis herpetiformis, trisomi 21, Turner’s syndrome and/or with ≥ 1 first-degree relative(s) with CD].
Analyses of serological and genetic markers (Paper 2)

Evaluating the serological screening strategy
Using the manufacturer’s recommended cut-off level for tTG-IgA (>5 U/mL), 151 fulfilled criteria for recommending a small intestinal biopsy and out of 147 biopsied, 134 CD cases were identified. By lowering the cut-off to tTG-IgA>4 U/mL, and recommending a biopsy for those with tTG-IgA 2-4 U/mL and EMA positivity, another 17 biopsy-verified cases were found. In addition, analysis of total Ig-A in 7161 children, with consecutive testing of tTG-IgG, identified another two cases (Figure 8). Hence, the strategy identified 153 CD cases among 192 fulfilling biopsy criteria (positive predictive value 0.8). Additional analysis of EMA helped to detect those needing a biopsy in the tTG-IgA level between 2-4 U/mL, but if EMA positivity were used as a criterion for biopsy also among those with tTG-IgA level between 4-20 U/mL, 2 cases would be missed (Paper 2, Table 2).

Analysis of genetic markers
All CD cases carried at least one CD-associated HLA-DQ haplotype. In the control material 55.7% of boys and 50.4% of girls carried either HLA-DQ2, HLA-DQ8 or both (Paper 2, Table 1). Sequential detection of alleles encoding for HLA-DQ2 or DQ8 in those with tTG-IgA>4 U/mL would have reduced the number of unnecessary biopsies by 2 (Paper 2, Table 2).

**Figure 8.** Serological screening strategy with number of children fulfilling criteria for recommending small intestinal biopsy (red boxes) and outcome in terms of identified CD cases. * Total s-IgA measured in 7161 children.
**tTG-IgA level and CD risk.**
The median (q1; q3) tTG-IgA level was 25.2 (9.13; 62.9) U/mL in the 153 CD cases and 0.10 (0.01; 0.20) U/mL in the 7055 non-CD children. The marker tTG-IgA had an area under curve on 0.988 in receiver operating characteristic curve calculated on the study population of 7208 children (Paper 2, figure 2).

Among the 184 children who were biopsied, the median (q1; q3) level of tTG-IgA in CD cases, which was 25.2 (9.13; 62.9) U/mL, were significantly higher compared to the median (q1; q3) value of tTG-IgA in the non-CD children that was 4.45 (3.10; 6.95) U/mL (Mann-Whitney, p<0.001) (Figure 9).

**Figure 9.** tTG-IgA levels in screening-detected CD cases and non-CD children in 184 children fulfilling serological criteria for recommending a small intestinal biopsy. The different cut-off levels (4 U/mL and 2 U/mL) are indicated as dashed lines and median tTG-IgA levels as continuous lines.

*Five children had low tTG-IgA but fulfilled serological criteria due to low s-IgA and tTG-IgG>6 U/mL.

As shown in the figure above, there were three children with tTG-IgA around 30 U/mL (range 29-32 U/mL) who had normal mucosa. All children with tTG-IgA>32 U/mL were diagnosed with CD. In those with a tTG-IgA level above 20 U/mL, 84 out of 87 (97%) received a CD diagnosis after small intestinal biopsy (Paper 2, Figure 3).
Experiences of receiving the diagnosis
The qualitative analyses of focus group discussions and written narratives, with both adolescents and their parents as informants, formed the basis for exploring their lived experiences of the CD mass screening, and are jointly summarized in Figure 10.

Figure 10. A model summarizing experiences of participating in a mass screening, receiving a CD-diagnosis, how the diagnosis may impact quality of life in terms of health benefits and social sacrifices, and attitudes towards CD mass screening.
The model shows how the reasoning behind participation was facilitated by a felt duty to contribute, reflected in the category “for the good of others”, but also by inducing feelings of insecurity, making the invitation “an offer hard to resist”. A notable immediate reaction to the diagnosis was that it felt “like a bolt of lightning”, but for some it provided an explanation of previous health problems, and “suddenly everything made sense”. The impact on quality of life was related both to changes in perceived health and to the adolescents’ experiences of living with CD in terms of social sacrifices. Changes in perceived health varied from “healthy as anyone else with no positive change” to “something was wrong and then changed for the better”, whereas experiences of living with CD ranged from “not a big deal” to “treatment not worth the price”. When looking back at the screening the most pronounced perception was “feeling grateful for being made aware”, as knowledge of a previously hidden diagnosis was perceived as important in itself, but also that it provided a means for feeling better. However, in contrast to this, some had “ambivalent feelings about personal benefits” and expressed disappointment and feelings of regret about having participated in the screening. The predominant attitude towards future screening was that it should be “a right for everyone” and be offered as early as possible in life. However, some felt screening was “only for sufferers” with symptoms, and a few were “questioning the benefits” overall.

The following text describes the results in more detail by highlighting each content area (heading) and elaborating on corresponding categories (in italics), presented together with quotations from the original text, to show how the interpretations are grounded in the data. As a complement, quantified measures of parents’ opinions about future CD screening are presented. The proportions of adolescents and parents who, in their narratives, supported the categories developed for some of the content areas are found in Paper 4, Table 2.

Reasoning behind participation (Paper 4)
Both adolescents and parents were aware that the screening was part of a research study and the category “for the good of others” reflects that the justification for participating was mainly based on willingness to help research, without considering potential personal implications. However, once the screening was offered, and a potential risk of having the disease was introduced, an element of insecurity was created. This insecurity, which was more prominent
among parents than among adolescents, led to wanting reassurance that the child was not suffering from the disease, and made the invitation “an offer hard to resist”. Peer pressure and parents deciding for them affected the adolescents’ decision-making, or rather their ability to decide for themselves.

“I felt more like everyone in my class was going to do it. Also my parents always sign all of that stuff. They just sign it and I should turn it in. So it was like this, because we have kind of a lot of such studies in our school. So it just felt completely natural.”
Girl, Narrative

Immediate reaction to the diagnosis (Paper 4)
A positive test result was rarely expected, and the majority of adolescents and parents therefore described how the news of the first test results (elevated serological markers) was met with great surprise and felt “like a bolt of lightning”. Some revealed that they even doubted it was correct and thought there might have been a mistake with mixed-up blood samples or the doctor phoning the wrong number. The adolescents described feeling left with a lot of questions, as their parents, who first gave them the information about the test results, were not able to answer all the questions that arose. This lack of knowledge fostered uncertainty that escalated into anxiety among both parents and adolescents.

“I didn’t know what gluten was and then they [the parents] said: By the way, your test results were high. Then I got really scared. Didn’t know what it was.”
Boy, FGD

Reflecting unpreparedness, there were descriptions of retrospectively feeling betrayed by the information given before the test, as the adolescents perceived that they had not been sufficiently prepared for the consequences of participating in the screening. They also described feelings of regret and disappointment with parents who had decided for them. The adolescents emphasized that more explicit information on possible consequences should be given before the tests and they also had suggestions about how such information could be.

“Before the test we didn’t receive much information about what it was and what it would entail if you had it, it didn’t say anything about what would happen if you were caught, like what would happen then? [...] There should be written information about how many will be detected, and if that happens it will be like this, but we just didn’t know.”
Girl, FGD
Another pronounced feeling was that the diagnosis suddenly transformed the adolescent from being normal to becoming different. Parents described how they felt that the screening took their healthy child away from them. For those who had not experienced any symptoms or signs before diagnosis, this transformation was even more abrupt.

Mother A: "Also, it's a little like when you have had a child who hasn't had any symptoms and you haven't had any idea, then they take a healthy child away from you when you get the diagnosis. It isn't health care's fault, and it's really good that you've found it, but it feels like they take a healthy child away from you."
Father B: "That's a good description, because that's exactly how it felt for us too."
FGD

Adolescents who were experiencing health problems before diagnosis, with parents who had the feeling that something was wrong with their adolescent, described how the diagnosis came as a relief and that “suddenly everything made sense”. For them, the diagnosis was like a puzzle where the pieces suddenly fit together.

“IT answered a lot of questions, because I was ill as a baby, and I have been to the doctor several times because of a stomach ache and so on”.
Girl, FGD

Both boys and girls described how they reacted with anger, anxiety, fear and sadness when receiving the diagnosis. Adolescents and parents expressed that the hardest part to handle was the fact that the disease was lifelong and that there was no cure. However, mothers of both symptomatic and asymptomatic adolescents also expressed feelings of guilt for not having suspected that their adolescent suffered from a disease.

“It was hard to learn that our daughter was sick, and that there was no cure, but a life-long disease, when you never had a clue or suspicion that it was even possible.”
Mother, Narrative
Changes in perceived health (Paper 3)
The adolescents and their parents described a large variation of signs and symptoms before diagnosis, and consequently the gluten-free diet had varying effects on perceived health. Three categories reflecting overall changes in perceived health were identified based on subcategories emerging from the adolescents’ own experiences and reinforced by overlapping subcategories based on parents’ observations (Paper 3, Table 3).

The category “healthy as anyone else with no positive change” reflects the experience of those feeling perfectly healthy before diagnosis, with no perceived positive change after initiated treatment. These adolescents were also considered to be healthy from the parental perspective.

“I felt good before and I felt good after so this wasn’t a big change for me.”
Boy, FGD

The category “retrospectively recognizing an improvement” refers to those who considered themselves healthy before diagnosis but when their wellbeing changed for the better after initiating a gluten-free diet, this gave them retrospective insight about previous symptoms. Interestingly, some adolescents and parents also stated that perhaps they were prone to identify previous symptoms and recognize an improvement to compensate for the difficulties that resulted from receiving the diagnosis.

“I had never had clear symptoms; sure I had been kind of tired during the day and didn’t want to be with friends after school. When we thought about it later, everything fell into place. It was my diet that had made me so tired [...] Now I feel much better. I am happier, have more energy and want to do more! Everything is so good now, I feel better, and school is working out great.”
Girl, Narrative

The category “something was wrong and then changed to the better” captured improved wellbeing among those with previous symptoms or signs of illness. Overall, physical, mental as well as behavioral symptoms were mentioned, and the parents or the doctor had sometimes blamed them on difficulties other than those that were health-related.

“My daughter has become totally different, more energetic and positive. She never has pain or discomfort in her stomach. Her mood has become much better”
Father, FGD
Adolescents’ perspective (Paper 3)
We found that the diagnosis was received and coped with differently among the adolescents, and together with related actions it resulted in different experiences of living with CD in terms of social consequences. Importantly, the adolescents’ attitudes and related actions seemed to be influenced by contextual factors rather than developing in direct relation to experiencing health benefits from the treatment. A situation where gluten-free food was easily accessible, or being served the same food as others, was perceived as convenient and reduced feelings of social deviance, whereas having to ask for gluten-free food or explain why they ate differently was perceived as bothersome and sometimes embarrassing. Poor availability when eating out with friends or when going on vacation was a common source of frustration. Parents, peers, teachers, school-kitchen staff and peers’ parents were pointed out as important significant others in providing support for the adolescents. The support was appreciated and seen both as part of caring and as a form of positive control.
Girl: "Hmm, I have a friend. She has had gluten intolerance since she was really little, and she is after me all the time, sometimes she'll send a text message, you're not eating gluten are you? I'm just like: Stop."
Moderator: "At the same time isn't it kind of good that someone reminds you?"
Girl: "Yeah, you feel a little better that she cares and doesn't assume that you should do it all yourself, and she's there for me anyway."

Girl A: "[...] then there are a lot of moms, so if you're going to eat there they go and buy gluten-free pasta and everything, and they are like oh, look at what I bought! You're just like, thanks."
Girl B: "Yeah, some people think it's fun to buy something different."
Boy C: "Yeah, it's like my friend, his dad always goes out and buys cinnamon rolls for me." (chuckles)
Boy C: "Always, so they always have gluten-free cinnamon rolls, before they used to make gluten-free food, his mom too, so they always have it."

The adolescents who belonged to a school class where others had also been diagnosed with CD described how this facilitated acceptance of the diagnosis and its consequences by inducing the feeling of being in this together.

"I have three [with CD] in my class, so it's like everyone understands. Because we're so many they all know; my closest friends know about it, and it's the same for the others. Then it's almost the whole class."
Boy, FGD

Four categories reflecting the variation in experiences of living with CD were seen, all with different levels of acceptance of the diagnosis and integration of the treatment into daily life (Paper 3, Table 4). These categories should be seen as typologies, or ideal types, that are grounded in empirical data.

Adolescents contributing to the category "not a big deal" considered CD in the light of its consequences, namely that you just have to stick to another diet. These adolescents reflected on CD by comparing it to other more serious diseases and thought that in comparison to a worse scenario having CD was not that difficult.

"It wasn't so shocking when I found out and I don't think gluten intolerance is a big problem for me. I mean, there are much worse diseases."
Girl, Narrative

Some adolescents had put up "a fight for normalization" as they did not like to be seen as different or to be treated differently than others. The adolescents contributing to this category perceived adhering to the gluten-free diet as inconvenient when away from home and asked
and wished for increased awareness about CD and the gluten-free diet. They identified the need for the scientific community to educate restaurant owners and teachers and wanted support, through newspapers and television, in their fight to be looked upon as “normal people”. They were also concerned about the fact that there were many people with undiagnosed CD and advocated screening to find more cases. These ‘CD ambassadors’ were active themselves in trying to educate friends, school personnel and restaurants about CD and the gluten-free diet.

“In school it’s also working OK, there have been problems when we go on field trips, for example; that they forgot to bring gluten-free hamburger buns for me. But we’ve talked with the school about it.”
Girl, Narrative

The category “a lonely struggle” represented the stigma felt by some of the adolescents, which resulted in efforts to conceal their CD. Asking for special food was associated with worrying about being seen as an outsider and feeling like a burden to others.

“My life became very different. When I am out or at my friend’s home I always have to keep track of exactly what I can eat. I play sports 4 times a week and if it’s a sport camp or another activity they always have to make special food for me. I’m scared that people will think I’m being difficult.”
Girl, Narrative

The main strategy for avoiding these reactions was to compensate by being overly nice and helpful. An alternative strategy for avoiding disclosure was to say that they were not hungry or just to eat the food offered, even if it was not gluten free. “The lonely struggle” category also included adolescents’ experiences of peers who became dominating and for whom the CD diagnosis became a stimulus for bullying.

Boy A: “I have some friends who are a little mean. They always want me to eat cookies or something, because they like it when I feel bad. (chuckle)
Girl B: “Nice friends you have!”
Boy A: “I’m not with them so much, but they just like it when people feel bad, like fight and stuff. One of them also has gluten intolerance. It’s him and others.”
Girl B: “So he tries to trick you?”
Boy A: “Yeah, exactly [...] but I know if there’s gluten in it, so I usually don’t eat it. But sometimes I do it anyway just so they’ll let me alone.”
FGD

Although it was not a predominant reaction, the adolescents contributing to the category “treatment not worth the price” had, after consideration, decided that adhering to the diet was too hard to
handle and perceived that “being different” was worse than suffering from symptoms.

"It was both fun and boring to know that I had gluten intolerance because earlier I had so many problems with stomach pain, but it was hard to be different. I thought it was hard with the gluten-free food. It wasn’t good and there were so many questions from everywhere. Finally I quit eating in school and avoided going out to eat with friends. Today I have totally quit the gluten free food. My stomach problems have come back but I feel better mentally. I can live a normal life now, except I have a little stomach pain.”

Girl, Narrative

Parents’ perspective (Thesis)
Parents made great efforts to support their adolescents in the different stages of acceptance and integration of their new life with CD. At home or when together with the family the parents played an important role as facilitators for the adolescent. However, in some important arenas such as at school or when with friends, they had no insight into how the adolescent managed, nor did they have much opportunity to offer support, which led them to feel that they had less control. In addition, adjusting to cooking the new gluten-free food was perceived as complicated by some and the gluten-free diet required the parents to watch over the adolescent in a manner they had not done before. Some parents expressed that they had become more protective and called themselves “worrywarts”. However, they also described feeling proud of their adolescents for how they managed the new situation and related how the adolescents were now favored with extra attention. The parents described how they tried to support their son or daughter and understand the various dilemmas they experienced. They also tried to respect the actions taken by the adolescent, but those whose child did not comply with the diet expressed how this gave them mixed feelings and generated anxiety about future complications.

Looking back at the screening (Paper 4)
The category “feeling grateful for being made aware” reflects the gratitude towards the screening that was expressed by adolescents and parents who perceived that becoming aware of a previously hidden disease was important in itself. However, the reasons for feeling gratitude differed. Either it provided a means for feeling better or, as asymptomatic adolescents and their parents expressed it, the screening was even more important for them, as otherwise they would never have known about the disease. Not having any suspicion and then realizing that their adolescent had the disease led to
feelings of insecurity and worry about what could have happened if they had not been in the screening.

“You’re happy when it comes out. Because she wasn’t sick, it’s even better that it came out now. It could have gone on forever”.
Mother, Narrative

Most adolescents and parents had adopted their doctor’s argument that adhering to the diet would help the adolescent to feel better and to avoid future health complications. Being concerned about these future complications functioned as a strong motivator for adhering to the gluten-free diet, even among those who were asymptomatic. They trusted the message and had internalized the risk for future complications, and only reflected further when probed about it. This was evident in the focus group discussions where the informants tended to be both surprised and confused when the interviewer posed an open question about whether they perceived the diagnosis as important or not. Interestingly, the complications mentioned by informants from different study sites differed from one another. In some study sites the greatest concern was the fear of getting diabetes, whereas in others cancer was brought up as the complication of most concern.

“I’m glad that I got to know because otherwise I would have gotten diabetes and I don’t want to have diabetes, because my cousin has diabetes and she thinks that it’s hard. So I’m glad I got to know, but I think it’s a shame that there wasn’t a chance for me to know about this earlier”.
Girl, Narrative

However, some adolescents and parents expressed “ambivalent feelings about personal benefits” of the screening. This reaction was related to having doubts about whether health complications really would occur if not adhering to the diet. Among the adolescents this attitude was also associated with difficulties in adhering to the diet and the absence of symptoms prior to diagnosis, whereas among parents it was related to worrying about the social consequences of adhering to a strict diet and to beliefs about a higher threshold for how much gluten a person can tolerate. Even if parents contributing to this category expressed doubts about the benefits of the treatment, the uncertainty of not knowing for sure if there would be future consequences resulted in ambivalent feelings so that they did not dare to take the risk and still intended to motivate their adolescents to comply with the diet, at least until they were adults.
Attitudes towards future screening (Paper 4)

From the parental questionnaire data we found that 92% of the responding parents wanted a CD screening to be implemented, whereas 2% were against it and 6% did not know (Paper 4, Table 3). The majority of parents (64%) wanted a screening to be conducted during the period from 0-10 years of age (Paper 4, Table 3). Analysis of the qualitative data shed light on the reasoning behind both adolescents’ and parents’ attitudes.

The category “a right for everyone”, reflecting the most common viewpoint regarding future CD mass screening on the part of both adolescents and parents, was strongly related to having internalized the risk of a possible [negative] outcome of untreated CD. It reflects an opinion stressing that if society knows how to find the disease, it is a human right to be offered the test. The informants expressed concerns about people who do not get the chance to know, and the adolescents in particular felt it was unfair that the screening study only approached sixth-graders in certain cities instead of being offered to all.

Girl A: “But what about those born in 1994 and 1995, won’t they have the test then?”
Moderator: “No”
Girl B: “I think that’s actually a bit silly, it would be better if it [the screening] was in all grades instead of just looking at us who were born in 93. Because then everyone would be able to have the test."
Girl C: “and then I think it will probably end up showing that quite a lot have it.”
Girl D: “Yes, because not everyone will notice that they feel sick from it, and then it’s better if they have the test, because otherwise there may be a lot of people who will never know.”
FGD

There was a consensus that a CD screening could contribute to avoiding future health problems among those who were unaware of their disease, but also that knowledge about a previously hidden disease was important in itself. Personal incentives for welcoming a screening for everyone were also found. The adolescents hoped that if more cases were found, the availability of gluten-free products would increase as would efforts from scientists to find a cure. A predominant opinion was that if a future CD screening was to be implemented, it should be conducted earlier in life. Adolescents thought that it would have been easier for them to adjust to the gluten-free diet if the CD had been found earlier, in that they would not have become accustomed to ‘all the nice food’ containing gluten. However, some advocated that the screening should take place in the teenage years, arguing that the person needs to be mature enough to
manage the transition from being normal to becoming ‘a celiac’, a transition experienced as a big step in life. Parents, on the other hand, advocated screening as early in life as possible with the hope of more effectively avoiding negative consequences of undetected disease. They were concerned that the untreated disease might influence the child’s growth and development more negatively if diagnosed during or after puberty. The parents also expressed how they perceived the teenage period to be filled with so many other commitments and distractions that it would be easier to adjust to the dietary recommendations if they got the diagnosis earlier. Some said that the timing of the screening (at 12 years of age) was the worse age to choose.

“We think it would be best to get the diagnosis as early in life as possible so that the transition to a gluten-free diet would not be so noticeable. The worst time to perform the general test must be at precisely this age when our daughter was tested. As a teenager, you absolutely don’t want to stand out and be different.”
Mother, Narrative

Some adolescents emphasized that although it is important to offer a screening test, it should be “only for sufferers“, those suffering from symptoms. This attitude was related to not having any short-term benefits from the treatment themselves and a belief that it would be superfluous for people and expensive for society to test everyone.

"I took the test but didn’t have any symptoms. Now I have to eat gluten-free. I just think that only those who feel bad should be tested. You can ask the students at the school if they feel bad, and if they have some symptoms then they can go to the school nurse and be tested”.
Boy, Narrative

Although it was not a predominant attitude, there were adolescents and parents who were “questioning the benefits” in general concerning the potential of a future CD mass screening. They were not convinced about the scientific basis for recommending a screening or the benefits of adhering to the treatment in the long run. Adolescents could also be doubtful because of their own experiences of finding it hard to adhere to the treatment when they had no immediate health benefits, and they did not want others to experience the same difficulties.

"Yes, I think it might be good to test all children for celiac disease. But on the other hand it depends, if it turns out that there are some (like me for example) who would have been able to eat normally and still not get any complications, and that they would eat a gluten-free diet needlessly for the rest of their life.
"Girl, Narrative
Comparing children’s and parents’ responses

Recognition of symptoms before diagnosis
(Paper 3 and thesis)
In the follow-up study with focus groups and narratives, the screening-detected CD adolescents and their parents retrospectively described a wide range of symptoms prior to diagnosis, with diversity in clinical presentation ranging from minimal (or absent) to severe (Paper 3). Symptoms described by the adolescents were feelings of low energy, tiredness, being angry, not growing well, being thin, mouth blisters, and stomach ache. Parents described having the feeling that something was wrong with their child and had observed symptoms such as fatigue, depression, paleness, dizziness, impaired growth, delayed puberty, being angry, short stature, stomach ache, diarrhea, frequent infections, headache, joint pain, and vomiting. Among adolescents indicating that their mood was different before diagnosis, we noted a pattern where girls described themselves as being extremely tired and having no energy, whereas boys described themselves as being in a bad overall mood and being angry (Paper 3).

Some parents had reflected that their son/daughter seemed to be tired or not feeling well, but thought it was because of other causes such as exercising a lot, difficulties with “becoming an adolescent” or just associated with the personality of their child.

“We wondered if he was bullied because he had stomach pain when he was supposed to go school and we didn’t understand why it was returning, so we just thought he had been bullied or something like that.”
Father, FGD

A few described having already noticed reactions to gluten-containing food during infancy, and others described how their son or daughter had never liked, or even avoided such food (e.g. pasta and bread). Also, a lower general intake of food was described.

“When I would give her regular baby formula I noticed that it didn’t sit well, so purely on intuition I gave her corn-based formula”.
Mother, FGD

Some had sought health care without the CD being detected. Out of those, some were left without an explanation while others were diagnosed with iron-deficiency anemia or given the explanation that the symptoms were related to psychosocial difficulties (paper 3).
The qualitative analysis signaled a variety of symptoms among the adolescents, but also a discrepancy between how the adolescents and their parents described the symptoms that we wanted to explore further. A preliminary analysis was performed, with questionnaires available from both the children and their parent(s) (n=130), in which questionnaire data on symptoms, reported prior to knowledge of CD status, in children who later became CD cases, were included in the estimates (Figure 11).

There were discrepancies in the proportions of children with symptoms when comparing responses from the children and from the parents, but only the symptom tiredness showed a statistically significant difference between the groups (McNemar’s test, p=0.029). However, the level of agreement between children and parents, as estimated by the kappa (K) statistic, ranged from -0.014 to 0.38 across the different questions; thus the observed level of agreement ranged from no agreement to slight agreement.

![Figure 11](image-url) Proportions of screening-detected CD children with symptoms prior to diagnosis, as reported by themselves (dark gray), and their parents (light gray), before knowledge of CD status.
Compliance with the gluten-free diet (Thesis)

As mentioned, the adolescents and their parents participated in different focus groups and from the moderator’s view it seemed as if parents sometimes had a different view of the adolescents’ compliance with the diet than how this was described by the adolescents. Additional analysis was performed based on data from the follow-up questionnaires, where the same question regarding the adolescent’s compliance with the gluten-free diet was posed to both the adolescents and the parents (Figure 12). A significant relationship between adolescent and parent ratings was found (Spearman’s rank correlation coefficient 0.405, p<0.001). A somewhat larger proportion of parents reported that their adolescent always ate gluten-free (79%) compared to 70% of the adolescents. The kappa(K)-value was 0.412, indicating fair agreement between the adolescents and their parents.

Figure 12. The adolescents’ compliance with the gluten-free diet, as reported by themselves (dark gray) and as reported by their parents (light gray).
Change in wellbeing (Thesis)

Additional analysis for the purpose of this thesis shows that when asking about the adolescent’s wellbeing today compared to before diagnosis, 54% of the adolescents reported improved wellbeing compared to 64% of the parents. Their answers showed a significant relationship (Spearman rank correlation coefficient 0.521, p<0.001), and the kappa(K)-value of 0.416 indicated fair agreement between adolescents and their parents (Figure 13). The adolescents’ wellbeing in relation to how they complied with the gluten-free diet is presented in Paper 3, Table 2.

![Bar chart showing the adolescents’ wellbeing today compared to before CD diagnosis, as reported by themselves (dark gray) and as reported by their parents (light gray).](image)

**Figure 13.** The adolescents’ wellbeing today compared to before CD diagnosis, as reported by themselves (dark gray) and as reported by their parents (light gray).
Methodological considerations

This thesis is based on research encompassing both quantitative and qualitative methodologies. For both methodologies it is of equal importance to reflect on how the design, sampling of participants, data collection, analysis and involved researchers have influenced the ability to capture the aims of the studies.

Strengths

The studies within this thesis have several strengths. The prospective collection of questionnaires allowed for describing frequency of symptoms in the children without being influenced by knowledge of CD status (Paper 1). Since we analyzed CD serological markers in all children, we were able to calculate the diagnostic accuracy of our questionnaire-based screening tool. The 12-year-olds who were invited represent about 10% of the Swedish 1993 birth cohort. We believe that the invited group is representative for the age cohort, as the study sites were located across Sweden and most study sites included all schools in the city itself as well as the surrounding countryside. The large-scale population-based screening gave a suitable option for evaluating the diagnostic accuracy of different serological screening strategies, since we applied testing of tTG-IgA and s-IgA in all children, as well as EMA-IgA testing in those with borderline values of tTG-IgA (Paper 2). The nested case-referent study allowed for evaluation of the possible role of detecting alleles encoding for HLA-DQ2 or HLA-DQ8 in future strategies for finding undiagnosed CD in the general population (Paper 2). Since the referents were randomly selected from the group of non-CD children and only matched for sex at the group level, we believe that they are representative for the general population when presented at the group level stratified by sex.

The follow-up study (Papers 3 and 4) was characterized by an emergent design, with triangulation of qualitative and quantitative approaches, enhancing the possibility to look at the concept of CD screening from different angles and with different data sources. The focus groups facilitated eliciting adolescents’ and parents’ views, and enabled exploration of attitudes, feelings and experiences at the group level, while the written narratives gave options for sharing more personal accounts and accessing individual experiences of the majority of informants. The components with quantification of narratives supporting different categories and presenting questionnaire data allowed for measures of the representativeness of some of the qualitative findings in the study population.
The extensive qualitative data material provided new insights, depth, and variations in experiences. To avoid losing important aspects, the large data material forced the qualitative analysis to be systematic and thorough in all steps. An audit trail with analytical memo notes and oscillation between data collection and analysis was maintained throughout the study. The integrity of the study was strengthened by the fact that the moderators were not involved in the health care provided to the adolescents.

Another strength is that at the time of the CD screening, as well as in the follow-up study, both children/adolescents and parents contributed with data, allowing us to explore their different views in questionnaires, narratives as well as in focus groups (Papers 1,3 and 4). We also made efforts to increase confidentiality between children and their parents by collect their questionnaires separately and conducting focus groups with children and parents in different groups.

Limitations
In the CD screening we invited a large number of children (n=10041) and 75% consented to participate. The Regional Ethical Review Board in Umeå recommended us not to approach those who declined participation in the study, and thereby we lack the possibility to explore whether characteristics of these non-participants differed from those of the participants.

Another limitation is that the questions on CD-associated symptoms and conditions used in the hypothetical screening tools were constructed for this study, and neither the reliability nor the validity of this part of the questionnaire was estimated (Paper 1). We decided that the children should fill in the first questionnaire in the classroom so that their reporting would not to be influenced by their parents. This may have influenced their responses, compared to if they had filled in the questionnaires at home or in a health care setting, but we are unable to assess in what way. The response alternatives to the questions on symptoms comprised five predetermined replies, and different methods for comparing the responses at the group level were explored. Symptoms were characterized as present for the responses “often” or “always”, and absent for responses “sometimes”, “seldom” or “never”, but the way in which these replies were dichotomized to symptoms perceived to be, or not to be, clinically relevant could be questioned. Given the broad spectrum of symptoms associated with CD, which in fact was also indicated by our qualitative follow-up study, children with undiagnosed CD may suffer
from other symptoms not asked for in our questionnaire. Thus, there may be symptomatic children whose symptoms were not reported and vice versa. The phrasing of the questions on symptoms varied slightly between the child and parental questionnaires as we adjusted the use of language for the children. The different phrasing may have had an impact on how they responded, and therefore the comparison of children’s and parents’ responses should be interpreted with caution. The hypothetical questionnaire-based screening tool in our study constitutes a different context than if this had been used “in reality”. In the study, the children (and parents) had already consented to have a blood sample analyzed for CD-markers. We do not know whether the children and parents would have replied differently to the questions if they had known that their responses would influence whether or not the child would undergo an investigation (having a blood sample analyzed) for CD. The associated conditions reported by the parents were not validated against medical records, and the accuracy of the information can be questioned. However, as the parents were the reporters and the diseases asked for in the questionnaires were well defined, we believe that their answers are reliable. We acknowledge that conditions other than those asked for may be associated with CD, and the way that we constructed the questions may have influenced the diagnostic accuracy of the questionnaire-based approach. Thus, questionnaires comprising other items may result in other conclusions.

Only children with elevated levels of CD-markers were referred for small intestinal biopsy (Paper 2). Also including children with Marsh I-II lesions as CD cases if having signs or symptoms indicative of CD might be controversial. Furthermore, among the children considered as non-CD children, with tTG-IgA<2U/mL, absence of disease was not confirmed by biopsy, and it is known that there are a few seronegative CD cases that will not be identified with conventional serological markers (115). A correct diagnosis, performed with a ‘gold-standard method’ (i.e. a small intestinal biopsy evaluation) is a prerequisite for evaluating screening tools. On the other hand, it would be unethical to perform small intestinal biopsies on all children included in the study. Also, the majority of cases had Marsh III lesions, and as the cut-off for the serological markers was set to prioritize sensitivity, and because of the large sample size including a large number of non-CD-children, we believe that we have reliable estimates of the diagnostic accuracy in terms of specificity, sensitivity and predictive values. Albeit a relatively large screening, this thesis
includes relatively small numbers of CD cases: (n=149) in Paper 1, (n=153) in Paper 2, and (n=130) and (n=107) when comparing children’s and parents’ responses in the thesis. Thus, the power of the study may constitute a limitation. In the ETICS study the necessary sample size was estimated for comparison of differences in CD prevalence between the two phases of the screening. Hence the power was not estimated for the hypothesis tested within the sub-studies presented in this thesis. Also, we have tested for relatively large numbers of variables and multiple testing increases the risk of finding significant differences by chance.

A limitation of the follow-up study (Papers 3 and 4) is that we did not invite those whose serological markers were positive but who declined further investigation, a group likely to be more negative towards mass screening than our informants. Also, willingness to participate in the focus groups may be influenced by more positive experiences of the screening. However, the narratives enabled us to collect information written individually, when not faced with a moderator, and in the instructions both to the focus groups and regarding the narratives we emphasized that all opinions were welcomed. As negative experiences were brought up, we believe that we provided an environment that also allowed for expressing negative feelings about the screening. Another limitation is that the follow-up study did not allow for exploration of differences between the experiences of participating in a research study compared to participating in a screening study offered routinely. Based on the results of our analysis, it is likely that the context of being invited to a research study influenced decision-making, reactions to the diagnosis, and experiences of health care in a way that may affect the transferability to another setting (i.e. to a routine mass screening).

As mentioned, the basis of the qualitative analysis comprised a large amount of data, and a limitation is that only the author of this thesis coded the data. However, to increase the credibility of the study, continual peer-debriefing sessions were held within the research group and a thorough systematic approach to the data-analysis was maintained. The quantified measures of individual narratives supporting the different categories (Paper 4, Table 2) should be seen as a complement to the qualitative findings, since informants may support a certain view without having expressed it in their narratives. However, the narratives do provide information concerning what the informants spontaneously brought up in their accounts.
Discussion

Main findings
This thesis shows that information on symptoms and CD-associated conditions were poor predictors for finding hitherto undiagnosed CD in the general population of Swedish 12-year-olds. Questionnaire-based case-finding by asking for symptoms and CD-associated conditions would have identified only 52 cases (38% of all cases) at a cost of blood-sampling 2282 children (37% of the study population). However, the serological marker tTG-IgA was an effective tool for identifying CD in the general population. We applied a cut-off lower than recommended by the manufacturer and identified several extra CD cases, showing that discrete elevation of the tTG-IgA level also needs to be taken into account. By adding complementary testing of HLA or EMA if tTG-IgA values were borderline, the diagnostic accuracy of the screening strategy was strengthened. However, measuring total s-IgA in almost all samples (n=7161, 99%), with consecutive analysis with tTG-IgG in those with low s-IgA levels, only discovered 2 additional cases, and this does not seem like an efficient strategy in a CD mass screening. All identified CD cases carried alleles encoding for either HLA-DQ2 or HLA-DQ8, as did more than 50% of the controls, which are believed to be representative for the general Swedish population.

Although the incentive to participate in the CD screening was found to be non-personal benefits, and the diagnosis was met with surprise, the most predominant reaction was a feeling of gratitude for being made aware of the diagnosis. Results from the follow-up study of screening-detected CD cases illustrate that 54% reported improved wellbeing after initiated treatment, but also that these health benefits had to be balanced against social sacrifices. A majority of parents (92%) welcomed a future screening, but both adolescents and parents suggested that it should be conducted earlier in life. This study contributes increased understanding concerning the acceptability of a CD screening among Swedish adolescents with CD detected through screening, indicating that even if some adolescents and parents were reluctant about screening, the most predominant view was that CD screening for everyone would be welcomed, with the argument that if we know how to detect the disease, being offered the test is a human right.
How to find undiagnosed celiac disease?
Recently published international guidelines suggest active CD case-finding by identifying and testing groups with an increased risk for CD (16). According to recommendations, testing with CD serological markers should be offered to all children who are seeking health care with any of the wide range of symptoms that should raise the suspicion of CD (e.g. failure to thrive, nausea, vomiting, abdominal pain, anemia, diarrhea or constipation). Testing should also be offered to children with conditions known to be associated with an increased risk for CD (e.g. type 1 diabetes, thyroid disease and Down syndrome) and to those with a family history of CD, even if they are asymptomatic.

Several studies have presented active case-finding strategies and concluded that they are effective by showing an increased incidence of CD in the targeted population. In an Italian study, education of doctors and introduction of a decision tool for CD case-finding within primary health care considerably increased the CD prevalence of the study population, but it still did not reach the known prevalence in the region (116). CD-marker testing of adult patients with symptoms or signs indicative of CD in primary health care has resulted in an increased CD incidence in Finland, Great Britain and the US (117-119). Nevertheless, none of the case-finding strategies suggested have attained the expected total prevalence of the disease, and they are limited by the lack of control groups. The sensitivity, specificity and predictive values of the suggested strategies therefore remain to be evaluated. To find the main part of unrecognized CD cases we probably need to approach the general population, and not only those seeking health care. Simple screening tools would be useful for identifying children in the general population with a higher risk of having CD.

In this thesis we explored strategies for finding CD in a general population of 12-year-olds and found that the prevalence of hitherto undiagnosed CD among those reporting symptoms was 2%, but even more importantly this prevalence was equal to that among those without symptoms (Paper 1). Asking for symptoms as a first screening tool had a sensitivity of only 34%, and a positive predictive value of 2%, and the majority of CD cases in our study population would have remained undiagnosed if an unselected screening had not been conducted. In a Danish population-based study, parents of 8 to 9-year-olds were approached with a questionnaire concerning 5
symptoms indicative of CD that was used to select children for blood sampling and consecutive testing of CD markers (93). The known CD prevalence in the study population doubled, but as the authors point out, without knowing the CD prevalence in the non-symptomatic children, who were not tested, the diagnostic accuracy of such a strategy cannot be assessed. Our findings complement the Danish study by suggesting that the CD prevalence is equally high among those without symptoms as it is in those with symptoms, and the number of cases found is proportional to the number of children tested, irrespective of reported symptoms. Our findings are in line with a recent CD screening study of adults in the US in which no gastrointestinal problems were found to be positively associated with CD seropositivity (81). Our findings are also in accordance with a recent Swedish study which found that among 26,180 children screened for CD within clinical practice, primarily by general practitioners or pediatricians (and presumably because of symptoms or conditions suggestive of CD), only 1.3% had CD (47). A systematic overview of diagnostic testing for CD among adult patients with abdominal symptoms within primary care concluded that gastrointestinal symptoms alone were not sufficiently accurate for predicting CD (120).

A screening tool asking for CD-associated conditions also had a poor diagnostic accuracy in our study population. If a questionnaire concerning CD-associated conditions were to be used as a first screening tool for CD, only 10% of hitherto undiagnosed CD cases would be identified (Paper 1). However, active case-finding policies for certain risk groups have already been implemented in Sweden, which was also reflected in our data by the fact that the children in the study who had already been diagnosed with CD were about four times more likely to have a CD-associated condition than the screening-detected cases. Thus, our findings reflect that the active case-finding strategy based on CD-associated conditions in Sweden seems to be effective, albeit not complete. In contrast, a Danish risk-group screening study found a high proportion of previously undiagnosed CD among children with type 1 diabetes (96).

The evaluation of screening tools using questionnaires on symptoms and associated conditions shows that unselected blood sampling and CD-marker analysis of everyone seems like a more efficient way to identify the majority of CD cases. Two main screening strategies based on blood sample analysis have previously been proposed (89). One has its starting point in identifying persons at genetic risk of
developing CD, thus those carrying necessary alleles encoding for HLA-DQ2 or HLA-DQ8. This risk group would then be further tested with serological markers, and theoretically this approach is suitable if a repeated screening is planned. In the other approach the whole population is screened directly with serological markers. Both strategies include a mandatory, verifying, small intestinal biopsy, which also is in concordance with the updated ESPGHAN guidelines for CD diagnostics (16). Both these screening strategies pose different practical and ethical dilemmas.

Interestingly, we found that more than 50% of the referents, believed to be representative for the general population, possessed the haplotype HLA-DQ2 or HLA-DQ8, or both (Paper 2), which is higher than the generally assumed prevalence of these CD risk alleles in Europe (35, 121). The high frequency of CD risk alleles in the Swedish population makes a screening strategy starting with HLA-DQ genotyping less efficient, as more than 50% will need further testing with CD markers and relatively few of them will develop CD. Such a strategy might also create unnecessary anxiety among those carrying the risk alleles, and studies on understanding the results of such testing in the general population are still lacking. On the other hand, fewer people will need repeated testing with such an approach, as the test will rule out the possibility of having CD in nearly 50% of the population.

In our screening study, we chose the second proposed strategy (serology first) by starting with analyzing tTG-IgA antibodies and s-IgA in all children (Paper 2). The marker tTG-IgA had an excellent diagnostic accuracy also when applied to the general population. All biopsied children with a tTG-IgA level above 32 U/mL had mucosal damage compatible with CD. The majority of the cases had a tTG-IgA level above the recommended cut-off value (5U/mL). However, a unique feature in this study is that we offered a biopsy to those with tTG-IgA>4U/mL and even in those with tTG-IgA>2U/mL if in combination with a positive EMA titer. In the group with tTG-IgA 2-4 U/mL and EMA positivity, we identified 10 CD cases in 20 biopsied children, indicating that discrete elevations of tTG-IgA levels also need to be taken into account and that the serum concentration of tTG-IgA should not be seen only as a positive or negative value. Current ESPGHAN guidelines recommend initial determination of s-IgA so as not to miss CD patients with specific IgA deficiency (16).
Previous economic evaluations have found that this is not cost effective in mass screening for CD (122), and in our study 2 cases were found at the cost of analyzing s-IgA in 7161 children (Paper 2).

In a screening situation, HLA-DQ genotyping of those with elevated levels of tTG-IgA would be more attractive than EMA-analysis, since the genotyping could be automatized and a negative result could be used to rule out the risk of developing CD in the future. In those with tTG-IgA>4U/mL, detection of alleles encoding for HLA-DQ reduced the number of unnecessary biopsies, although to a lesser extent than using EMA, but on the other hand without missing any CD case (Paper 2, Table 2).

**Experiences of receiving a diagnosis in a screening**

**Invited and sieved out**

To the best of our knowledge the qualitative follow-up study presented in this thesis is the first to explore experiences of receiving a CD diagnosis in a mass screening. We found that the reasons for adolescents and parents to participate in the screening involved a feeling of duty to contribute to research as well as a means of handling the risk they were introduced to (Paper 4). Their idea that participation would lead to greater benefits for everyone most likely reflects societal norms to help others. These findings are in line with results found in a previous qualitative ETICS sub-study involving adolescents who had not yet received their test results (94). However, in that study the adolescents felt involved, well informed and perceived that they had a general understanding about CD. Contrary to this, we found that some adolescents who received the diagnosis felt, in retrospect, that they had not participated in the decision to take part in the screening. They also felt that they had not been provided with enough information about the possible consequences of their participation and expressed a need for improved information before the test. These results imply that it is probably not until being diagnosed that the consequences are fully incorporated and detailed information is sought. Nevertheless, this underlines the importance of true informed consent, which is especially challenging when approaching minors and their guardians. However, the information provided when inviting persons to CD screening programs must be balanced to avoid unnecessary anxiety while waiting for the test results, since the majority of those participating in the screening will not be diagnosed with the disease.
Being surprised, feeling angry and sad, or even questioning if the test results were correct characterized the initial reaction to the diagnosis (Paper 4). Later these feelings developed into a belief in the benefits of becoming aware. The emotional responses of denial, anger, and later acceptance correspond to stages of grief first described by Elisabeth Kübler-Ross (123). As most adolescents and parents had no suspicion about the disease, they felt unprepared. Lack of sufficient preparation for receiving “bad news” has also been observed in studies of other screening-detected diagnoses (124, 125). Having a moderate amount of concern prior to a stressful event (proactive coping) is suggested to facilitate the psychological adaptation once the event occurs (126). As a screening-detected diagnosis is often unexpected, and the transition from being healthy to becoming a patient is abrupt, this probably influences the psychological adaptation process negatively. Healthcare providers therefore need to be sensitive to what screening-detected patients actually know about their disease, and how they cope with the diagnosis, in order to provide adequate support and follow-up care. Overall, boys and girls seemed to have similar reactions towards receiving the diagnosis. However, we found that mothers, compared to fathers, were more prone to express feelings of guilt for not previously having suspected what their child was suffering from. This gender difference in parental coping has been observed in other studies (127, 128).

Perceived health before diagnosis
We found a large variety of recognized symptoms before diagnosis (Paper 3), and our results are supported by other studies showing that true symptomatic cases are also found among screening-detected CD cases (96, 129, 130) Our findings that some had experienced health problems, and sought health care without receiving a correct diagnosis (Paper 3), indicate that further educational efforts to increase CD awareness are needed. Hence, being “screening-detected” does not necessarily mean being asymptomatic. However, we also found that the frequency of symptoms among screening-detected CD children is similar to that in non-CD children when reported prior to knowledge of CD status (Paper 1). In fact, the CD cases participating in this study also rated their health-related quality of life, measured by EQ-5D instrument, as similar to that of their peers prior to knowledge of their CD status (131). These findings are in line with a study of Hoffenberg et al, who showed that before knowledge of CD status the number of symptoms reported among CD cases was similar to that in the control group (130). Interestingly, they also showed that after knowledge of
elevated CD markers a significantly greater number of symptoms were reported (130). We also observed the phenomenon of retrospective recognition of symptoms in relation to a screening-detected CD diagnosis (Paper 3). This reflected the experience of becoming aware of symptoms first when perceiving improved health, but interestingly, some adolescents and parents also stated that perhaps they were prone to identify previous symptoms to justify that something good came out of receiving the diagnosis (Paper 3). Thus, probably the retrospective recognition of symptoms reflects both an increased understanding of symptoms and reassurance about the benefits of having received the diagnosis. When comparing the children’s and parents’ responses concerning symptoms prior to knowledge of CD status, the proportion of children with symptoms was higher when they themselves were asked about this, compared to when their parents were asked (Thesis).

Considered together, our different data sources comprising responses to prospectively and retrospectively posed questions, as well as quantitative and qualitative inquiries with information from both adolescents and parents, show that CD may present in many different ways, and the type of data source significantly affects the measures provided.

**Impact on quality of life**

We showed that 54% of children with screening-detected CD reported improved wellbeing one year after initiated treatment (Paper 3). In line with our results, a 10-year follow-up study of screening-detected CD children showed improved health status in 66% of the treated children (70). However, in our study we also found that the diagnosis had varying impact on quality of life that related both to changes in perceived health and to the adolescents’ experiences of living with CD in terms of social sacrifices (Paper 3). With a few exceptions (58, 76), previous research on CD and the gluten-free diet’s effect on children’s and adolescents’ quality of life has mainly utilized quantitative methods and involved clinically detected CD cases (69-75). The only study on how a screening-detected CD diagnosis and treatment may impact quality of life involved information from parents of screening-detected CD children diagnosed at the age of 2 to 4 years (70). They showed that at diagnosis, health-related quality of life among those with symptoms was lower than among referents, and improved significantly after one year on a gluten-free diet. The screening-detected CD children...
without symptoms had a health-related quality of life similar to that of the referents both at diagnosis and at the one-year follow-up (70).

Although the tools developed to quantitatively measure quality of life may facilitate reproducibility, they do not allow for capturing the complexity of the patients' lived experiences and have a concomitant risk of not covering all the factors influencing quality of life (132). By using qualitative methods, our study accessed adolescents' and parents' own perspectives, which allowed for a holistic description of changes in perceived health as well as the impact on daily life. In this study we observed a varying impact on quality of life in terms of social sacrifices experienced by the adolescents. Whereas some had, or were provided with, tools to successfully manage daily life, others found CD to be truly burdensome with considerable negative impact on their lives. A predominant experience was that adhering to the dietary restrictions limited daily life and caused feelings of being a burden or an outsider. Other studies have also shown that the lifelong dietary restrictions have considerable impact on daily life, and strict compliance is difficult to achieve (56, 57, 69, 133-135). We saw that adhering to the gluten-free diet seemed to be related to felt stigma (136). In line with Goffman’s work on stigma management (137), we found that the adolescents had adopted strategies such as withdrawing from social contacts, attempting to hide their condition, or compensating by being overly nice. These findings build on the findings of another study on clinically diagnosed adolescents, which reports on stigma experiences related to adhering to a gluten-free diet (76), by indicating that the mode of diagnosis probably does not affect stigma experiences. Our results also indicated that stigma experiences may be linked to gender differences in management strategies. In general, boys described more efforts to conceal their disease and reluctance to incorporate the disease into their social identities than girls. However, those who had chosen to abandon the gluten-free diet were girls. We saw a tendency for boys to ask for support in their efforts to change external structures, whereas girls took on an active role themselves. These results are in line with studies about adolescents with asthma and diabetes showing that gendered meanings of stigma influence the strategies used to cope with the disease and treatment (138).

Acceptability of a mass screening
This thesis contributes to an increased understanding of the acceptability of CD mass screening among those being diagnosed, and their parents (Paper 4). They expressed gratitude for becoming aware of a previously hidden disease, based either on experiences of
improved health after initiated treatment or adaptation to the risks of what otherwise could have happened. In fact, those who were asymptomatic before diagnosis, and their parents, seemed even more prone to advocate screening, as it would be the only way to identify their disease. We also observed that the individual doctor’s view of risk strongly influenced the informants, since the risks mentioned differed between study sites. The informants’ accounts reflect how the screening itself produced concerns, resulting in increased risk awareness during the screening process. Implementation of screening programs in society as a means of preventing complications could be seen as part of the modern risk society described by Beck (139). In our study, some informants had ambivalent feelings about the personal benefits. According to Beck this can be seen as a consequence of the modern risk society where increased awareness of risk is followed by an increased capability to question the suggested risks. It is often people themselves who start to reflect on risks, since it becomes harder to rely on scientists to do this for them.

In our study some informants questioned the benefits of the CD screening and asked for more scientific evidence about the consequences of exposing the population to a mass screening. However, most adolescents and parents responded that if there are means to find the disease, then everyone should have the right to be offered the test (Paper 4). Screening to identify undiagnosed CD was seen as beneficial for health outcomes, but the diagnosis was also important in itself. The latter finding relates to the ethical considerations introduced by genetic screening tests that are increasingly advocated, where preventive measures are sometimes not available (140). If information about a diagnosis (or carrier status) is in itself viewed as a right and as sufficient for advocating screening, some of the currently accepted principles for screening will be ruled out. Thus, the challenge with mass screening is that the presumed “right to know” must be balanced against the principle of non-maleficence, and the autonomy of individuals with a right to choose not to know.

Who holds the truth?
In the qualitative data we found discrepancies in recognized symptoms before diagnosis (Paper 3). Adolescents and parents tended to describe symptoms with different wording and had interpreted the cause of the symptoms differently. Interestingly, when comparing the frequency of the children’s symptoms before diagnosis
as reported by the children themselves compared to their parents’ reports, we also found disagreements between children’s and parents’ reporting (Figure 11). In general, the children as a group reported a higher proportion of symptoms compared to their parents as a group. In fact, we found that the level of agreement between children and their parents ranged from no agreement to fair agreement. In contrast to this, a recent Swedish study reported that parents of CD children valued their health-related quality of life as lower than the children themselves did (75). Further, in a study of children’s pain after surgery, parents tended to underestimate the child’s pain after surgery, and poor agreement between children and parents was also indicated (141).

Should celiac disease be added to the list of diseases screened for in the general population of Sweden?

So where do we stand today? Should CD be added to the list of diseases screened for in the Swedish general population? To answer that question, let us go back and evaluate CD as a candidate for mass screening in the light of the proposed criteria set up by Wilson and Jungner (Table 1)(3).

First, the condition sought should be considered as an important health problem and the natural history of the condition should be adequately understood (Principles 1 and 7). The concept “important health problem” does not necessarily mean that it is common, although that would generally be the usual requirement. Rather it implies that the course of the disease is associated with severe complications if left untreated. Also the importance of the health problem needs to be considered from the point of view of both the individual and society (3). CD is a common chronic disorder and untreated clinically-detected CD is associated with increased risk of negative health consequences such as anemia, short stature, delayed puberty, depression, and low bone mineral density (18). However, less is known concerning the natural history of screening-detected CD. A Dutch follow-up study of screening-detected CD children showed that among those with no symptoms at diagnosis and who remained on a normal diet, 25% developed symptoms and evidence of a clinically active disease during a 10-year follow-up period (70). Studies on mortality risk for individuals with unrecognized CD (most often in terms of elevated serological markers) show
divergent results. Some show an increased mortality risk among individuals with positive CD serology compared to those with negative serology (142-144), and a Swedish study even showed that patients with positive CD serology, but normal small intestinal architecture revealed in biopsy, had an increased mortality risk (145), while others have not confirmed an association between positive CD serology and an increased mortality risk (146-148). Thus, additional studies on long-term effects of untreated screening-detected CD on co-morbidity and mortality are needed to clarify the potential benefits of treating CD detected early through mass screening.

An accepted treatment, that gives a better prognosis if given early, and an agreed-upon policy concerning whom to treat as patients, should be available (Principles 2 and 8). In symptomatic CD patients adherence to a gluten-free diet improves wellbeing (61), restore mucosal damage (149) and ameliorates complications like low bone density (150, 151). However, the effect of a gluten-free diet on screening-detected CD patients has been debated (152). Children with Type 1 diabetes and screening-detected CD showed improved nutritional status and symptom alleviation after 2 years on a gluten-free diet (96). However, although the CD was screening-detected, the majority of the children actually had symptoms before the CD diagnosis (96). A Finnish study showed improved quality of life and a reduction of gastrointestinal symptoms among adults with screening-detected CD (51), whereas a study from the UK showed no difference in quality of life in screening-detected cases when compared with the general population at baseline and follow-up (59). A common argument against CD screening is that strict compliance with a gluten-free diet is hard to achieve in symptomatic CD patients, and even harder in those presumed to be asymptomatic (83, 153). In our study, strict compliance with the gluten-free diet was reported by about 70% of the adolescents (Paper 3). Indeed, we found that experiencing health improvements after initiating the gluten-free diet functioned as a motivator for adherence (Paper 4). However, even if the adolescent’s health had not improved, most adolescents and parents expressed that avoiding future health complications motivated dietary compliance (Paper 4). In addition, adhering to the diet was perceived as more important than following health promotion messages aimed at society as a whole, since CD was perceived as more of a personal threat. Previous studies have shown that compliance with a gluten-free diet among adolescents is higher when CD is diagnosed earlier in life due to symptoms (154). In our study, both adolescents and parents suggested that the screening should be
conducted earlier, with one of the arguments being that adhering to the diet would be facilitated by receiving the diagnosis earlier in life (Paper 4). However, the optimal age(s) for testing for CD is yet to be determined and this will also require knowledge concerning the age distribution for disease initiation (sero-conversion). Thus, multi-country birth cohort studies with repeated blood-sampling for analysis of CD serological markers are needed, and such studies are underway (100, 155). As discussed earlier, clear evidence on whether treatment at an early stage is more beneficial than at a later stage is still lacking, and before implementing a CD screening, further research is needed to evaluate the extent to which treatment of screening-detected CD reduces long-term negative health consequences, as well as factors facilitating adherence to the gluten-free diet.

Facilities for diagnosis and treatment should be available (Principle 3). In Sweden we have facilities for offering small intestinal biopsies, although current facilities need to be expanded in order to handle the increased flow of patients. Adhering to the treatment with a gluten-free diet is demanding for the patients and it would be advisable to allocate resources for facilitating support for the patients and develop supportive tools to facilitate compliance. Recently, a randomized controlled trial showed that patient education, compared to usual care, significantly increased psychological wellbeing in women who had been treated with a gluten-free diet for more than 20 years (156). It is possible that educational efforts may be even more effective if carried out early after diagnosis, and such studies should preferably also be conducted focusing on screening-detected CD children and adolescents.

There should be a recognizable latent or early stage of the condition, and a suitable test or examination to detect this stage, which also is acceptable to the population (Principles 4, 5, and 6). Hence, to avoid false positive tests and missed diagnoses, screening tests with high diagnostic accuracy must be available. The serological CD-marker repertoire offers an excellent method for recognizing CD at a latent or early symptomatic stage, and is therefore a suitable screening test. We have shown that the marker tTG-IgA worked well when applying the test to the general population (Paper 2). The blood sampling for serological markers seems fairly acceptable to children (94), and considered together, suitable screening tools for CD are available.
The cost of finding the cases should be economically balanced in relation to possible expenditures for medical care as a whole (Principle 9). A few health-economic evaluations have been published (46, 157, 158), but further evaluations are needed specifically for CD mass screening. Mass screening should constitute a wise use of available societal resources, compared to what the resources could otherwise be used for, and it therefore also needs to be compared to other public health interventions.

In their tenth criterion, Wilson and Jungner stress that a mass screening should not be a single-occasion project, as only those with the condition at that particular time would then be identified. Such approaches are currently used in Sweden (within the framework of research studies), but if it is formally implemented, CD mass screening would need a continuing and gradually built-up organization.

The classical screening criteria posed by Wilson and Jungner lack a criterion specifically addressing acceptability of the diagnosis and its psychological, ethical and social implications for those being diagnosed in a screening. This criterion comprises the important idea that the diagnosis and treatment following a positive result should be acceptable to the population addressed by the screening. A common argument against CD mass screening is that the diagnosis and treatment would be harder to accept and manage among those experiencing no prior symptoms compared to patients with clinically-detected CD. This assumes that screening-detected CD cases do not experience symptoms, while we have shown that screening also captures unrecognized symptomatic cases (Papers 1 and 3). Furthermore, it assumes that experiencing health improvement facilitates acceptance of the diagnosis. In a Finnish study, screening-detected CD adults reported improvement in self-perceived health and quality of life after diagnosis, but a sub-analysis of asymptomatic screening-detected CD adults showed that self-perceived health decreased and their concern about health increased after diagnosis (61). Contrary to this, we found that the adolescents’ feelings and attitudes about living with CD did not have a direct relation to whether or not they experienced health improvement (Paper 3). Those with great health benefits could be the ones suffering most in terms of social consequences, and vice versa, indicating that there are many aspects, apart from perceived health benefits, that influence the adolescents’ experiences. Without feeling prepared, the adolescents and their parents suddenly encountered a life-long disease that
affected their daily life both practically and socially, but they still felt
gratitude for the screening, and that the diagnosis had been revealed
(Paper 4). They also welcomed future CD screening for others with
the argument that if means for finding the disease are available,
people should have a right to be offered the test (Paper 4). Thus, a
CD screening as a public health intervention needs to be evaluated
by balancing the intended positive outcome in terms of health
benefits, for example, against unintended negative consequences in
terms of social sacrifices, for example (159, 160). Further qualitative
studies on psychological and social reactions, as well as attitudes
and feelings about a CD screening, are needed to fully understand
the implications for designing and evaluating full-scale screening
programs among children or adolescents. Such studies should
preferably also involve other age groups and cultural settings. In
conclusion, before implementing a mass screening for CD we need
further evidence to ensure that the potential benefits outweigh the
harm (and costs) both for involved individuals and society.
Concluding remarks and future prospects

This thesis contributes increased knowledge about strategies for finding undiagnosed CD children in the general population, and has explored the effect of a CD mass screening among those who are directly affected, namely those receiving the diagnosis.

Asking for CD-associated symptoms and/or conditions has a poor diagnostic accuracy for finding hitherto undiagnosed CD in the general population of Swedish 12-year-olds. However, there is a need for further attempts to develop simple and non-invasive tools for finding undiagnosed CD, such as by including other types of questions addressing additional signs or symptoms.

The CD-marker tTG-IgA is well suited for finding undiagnosed CD in the general population. Detection of alleles encoding for HLA-DQ2 or HLA-DQ8 may be used in those with elevated CD-markers in order to reduce unnecessary small intestinal biopsy investigations, but does not seem suitable as a first step in a Swedish mass screening because of the high frequency of CD-risk alleles in the general population. However, adding non-HLA variants to the HLA prediction improves the genetic risk assessment and may be an option, although such an approach carries extensive ethical and practical considerations that need to be well scrutinized before implementation. Our recommendation for future mass screening efforts is therefore to start with blood sampling of all persons in the target population and analyzing tTG-IgA as a first step.

The screening-detected CD diagnosis has varying impact on adolescents’ quality of life, where their perceived change in health has to be balanced against the social sacrifices that the diagnosis may cause. This needs to be taken into account in any future suggestions for CD mass screening and in the management of these patients. Further research on interventions for facilitating daily life for CD patients are needed, such as regarding the impact of educational efforts on school personnel (especially in home economics and school cafeterias), who were identified by the CD adolescents as important significant others.

The experience of receiving a CD diagnosis in a mass screening was previously unexplored. This thesis takes a first step in increasing the understanding of CD-screening acceptability from the perspective of newly diagnosed adolescents and their parents in a Swedish context. Although some of our results may possibly be transferable to CD
mass screenings in other settings, there is a need for additional studies on the acceptability of CD screening that involve other age groups and cultural settings, as well as those individuals found to have false positive results in a screening.

In this thesis, different data sources were used for exploring both the CD children/adolescents’ and their parents’ perceptions of symptoms prior to diagnosis. We found a relatively poor agreement between the two. Further research on “Who holds the truth?” is warranted, especially if asking for symptoms is intended to guide further CD investigation.

Whether or not a CD mass screening should be implemented in Sweden remains to be further evaluated. We need more evidence on the long-term consequences of treating ‘asymptomatic’ screening-detected CD cases, and we need to assess whether such intervention is motivated when compared to what the resources could otherwise be used for. If CD mass screening is to be implemented, it is crucial to determine the target population’s optimal age (or ages) for invitation to attain a balance between identifying the majority of cases and not having to repeat the screening many times.

A crucial issue is also to identify who should decide about whether or not a CD mass screening should be implemented in Sweden. Ultimately, the decisions to develop, implement and continue to fund mass screening programs are political. Today Sweden lacks a centralized organization that evaluates new suggestions for mass screening efforts, or that offers means for follow-up of programs that are already implemented (161). The Swedish National Board of Health and Welfare has been assigned to develop a national model for overseeing mass screening efforts for cancer. Possibly the model will later be developed as a generic model to evaluate mass screening programs for conditions other than cancer, for example within the child welfare system. Even if decisions on implementing screening programs are made at a regional level, it is of utmost importance to have a centralized organization that issues recommendations on mass screening to assure that present and future screening programs are conducted so that the benefits outweigh the harm they may cause, but also to allow for access to health care on equal terms, irrespective of which county council a person happens to live in.
Another critical issue related to early detection of disease is the increasing business of direct to consumer medical testing, which also include genetic testing. Such testing is offered at the initiative of the commercial sector and is clearly driven by other values and incentives than when screening programs are offered by society or health care. Regulations guaranteeing safety and quality are needed as these actors are increasingly entering the “health market”. People today have access to various screening tests and predictive genetic tests, with a concomitant risk of finding abnormalities. These tests should fulfill ethical requirements by balancing the possible harms and benefits of the products. After all, the more examinations a person undergoes, the higher the risk of finding deviant result is. Or, as phrased by one of the parents in our study:

“Well, they sometimes say that those who are healthy have really just not been examined closely enough.”
Personal reflections from the researcher

As a young medical student my goal for the future was to work as a medical doctor in parts of the world where I thought I would be most useful. In line with these plans I applied, and received, a scholarship for a clinical visit at the Oshakati state hospital in Namibia in 1997. This was my first clinical practice, an intense, scary and very rewarding time for me. My breaks between clinical duties were spent in a habilitation center for malnourished children. In this setting, where resources were scarce, and where “small and simple” measures like educating parents in basic child nutrition could actually prevent serious conditions, my interest in prevention and public health flourished. While continuing my studies at medical school after returning from Namibia, I therefore contacted Epidemiology and Public Health (nowadays called Epidemiology and Global Health) in Umeå and expressed my interest in continuing my work within the field of child nutrition. In the evenings I studied tropical medicine. Together with researchers from Nicaragua we planned a survey to determine the prevalence of malnutrition among small Nicaraguan children. With support from a Minor Field Study scholarship from SIDA, I went to Nicaragua for three months to carry out my first fieldwork within epidemiology. With a setting very different from what I was used to, I found myself leading the data collection, with seven fieldworkers (all of them older than I), searching for 758 children in the municipalities of Leon and surroundings. The three months of data collection eventually resulted in a report, “Prevalence and factors involved in stunting of children two to five years of age in the municipality of León, Nicaragua, 1998.” Although this experience was valuable, what still concerns me is that we only determined the extent of the problem, but had not planned for any preventive measures within the frame of our study. I would do that differently today. Nevertheless, my interest in public health was forever firmly established. After my work in Nicaragua I completed medical school and an internship (and had our first child). Thereafter I started my specialist training at Clinical Genetics, Umeå University Hospital, started to work as a project assistant within the ETICS-study (and had our second child). Why not do all of it at the same time?!

The plans for my PhD project were to combine genetic and epidemiological studies, but when the first field phase of the ETICS-study was finalized the research group discussed also exploring how the participants felt about receiving the diagnosis. We thought it might be difficult to capture that through questionnaires and decided to use
a qualitative approach. I was assigned this mission. So, without having any idea about what qualitative methodology was, I found myself starting up and planning for the qualitative studies included in this thesis. To facilitate the process, or actually to secure the process, I attended different courses on qualitative methodology. A new world opened up to me. I still wonder how this methodology can be invisible in medical school, given that during our clinical work we face individuals with feelings and experiences all day long. After a while, when I had overcome my own doubts, I found myself targeted by the skepticism of others. How can this be science? Where are the figures and p-values? Can you as a medical doctor do qualitative research? You don’t seem to have any theoretical framework! In settings with other qualitative researchers I was an odd bird, and in settings with other quantitative researchers I was also an odd bird. While working within genetics, the field of epidemiology is sometimes questioned, and while working within epidemiology, genetics is seen as very technical, expensive and without relevance for public health. There have naturally been times during my research training when I have felt that my research is too far from my clinical work. CD patients are mostly handled by pediatricians, internal medicine practitioners, or general practitioners, but certainly not by clinical geneticists. In the end there are genetic tests for CD, mass screening is offered for monogenic diseases, I meet patients who have received a diagnosis pre-symptomatically (like some of those I study), and I teach medical students about qualitative research methodology. For me personally, the pieces have finally come together.

From my point of view I have never understood the problem with being diversified. Certainly, taking my PhD training as an example, I will not have the depth in qualitative methodology that a social scientist has, or the depth in genetics that a molecular geneticist has, or the depth in epidemiology that an epidemiologist has. But instead I (hopefully) have achieved breadth in my knowledge. The process of finalizing a PhD thesis involves acquiring skills and collecting them in a future research toolbox. Where my toolbox and I will go after the completion of this thesis is yet to be determined, but I am ready. I am not interested in debates about which field is most important. My “theoretical framework” is pragmatic, simple and straightforward: The research question steers which method that is suitable for responding a certain research question. Now I am prepared to pose new questions, open my toolbox and see what I find.
Svensk sammanfattning

Bakgrund till och syfte med avhandlingen

Celiaki, även kallat glutenintolerans, är en kronisk sjukdom och betraktas nu som ett folkhälsoproblem. Ärtliga faktorer spelar en avgörande roll i utvecklandet av sjukdomen, men även livsstilsfaktorer påverkar risken att insjukna. Hos personer med celiaki orsakar gluten i kosten en inflammatorisk reaktion resulterande i atrofi av tunntarmsслемhinnan och därmed försämrat upptag av näringsämnen. Celiaki kan debutera i såväl småbarnsåren som i vuxen ålder. Små barn med obehandlad celiaki kan vara gnälliga, ha mag-tarmbesvär och dålig tillväxt. Hos ungdomar och vuxna ses varierande symtom såsom trötthet, magont, diarré, förstoppning, och anemi. Sjukdomen kan också förekomma utan symtom. Serologiska markörer används i utredning av celiaki, men för att säkerställa diagnos behövs oftast en tunntarmsbiopsi. Rekommenderad behandling - att för resten av livet helt utesluta alla glutenhaltiga livsmedel - innebär praktiska, ekonomiska och sociala konsekvenser. Celiaki-förekomsten i olika befolkningar varierar mellan 0.3% till 3% där Sverige ligger inom det övre spannet.

Deltagare och metod
Under läsåret 2005-2006 genomfördes en skolbaserad screening för celiaki i fem orter i Sverige. Av 10041 inbjudna tolvåringar, erhölls blodprov från 7208 (72%) barn. Blodproven analyserades för serologiska markörer som vid förhöjda värden kan indikera celiaki (antikroppar mot vävnadstransglutaminas, tTG-IgA samt endomysium, EMA) samt för total s-IgA. Innan barnen och föräldrarna hade fått kändedom om provsvaret fick de skatta barnets symtom i individuellt ifyllda enkäter. Föräldrarna fick även rapportera om barnets övriga sjukdomar samt familjehistoria med avseende på celiaki. Frågeformulär erhölls från totalt 7054 (98%) barn och 6294 (88%) föräldrar. Totalt fann vi 192 barn med förhöjda nivåer på markörerna, varav 153 fick sin celiaki bekräftad via tunntarmsbiopsi.

Alla barn som fick diagnosen celiaki bekräftad via screeningen, samt deras föräldrar, inbjöds till en uppföljningsstudie då barnet haft diagnosen i cirka ett år. I gruppdiskussioner och skrivna berättelser ombads både barn och föräldrar att dela med sig av sina erfarenheter kring att ha fått kändedom om barnets diagnos, hur livet och barnets hälsa förändrats efter kostomläggningen, samt deras attityder kring allmän testning för celiaki. I enkäterna ombads både barn och föräldrar att skatta barnets följsamhet till behandlingen samt huruvida barnets välbefinnande förändrats efter kostomläggning. Föräldrarna tillfrågades även om attityder kring screening med kortsvarsfrågor. Totalt erhölls information om 117 barn, endera från dem själva (n=101) eller från deras föräldrar (n=125). Data analyserades med både kvantitativa och kvalitativa metoder.

Resultat
Symtom var lika vanligt hos barn med screening-upptäckt celiaki som hos barn utan celiaki, och celiaki var lika vanligt hos symtomatiska barn som hos barn utan symtom. Om förekomst av ett eller flera symtom och/eller associerade sjukdomar eller årtätighet för celiaki hade använts som ett första screening instrument hade 52 fall (38% av alla fall i studiepopulationen) diagnostiserats efter analys av blodprov på 2282 barn (37% av hela studiepopulationen). Vi fann dock att analys av tTG-IgA var ett utmärkt första screening instrument med god diagnostisk säkerhet även i en allmän screening. Vi sänktes cut-off för tTG-IgA från den rekommenderade nivån 5 U/mL till 4 U/mL och genomförde kompletterande analyser av EMA hos barn med tTG-IgA 2-4 U/mL. Därmed identifierades 17 ytterligare fall på bekostnad av 32 barn som biopserades. Genom att mäta total s-IgA
och analysera celiaki-markörer baserade på IgG-antikroppar hos de med låga s-IgA nivåer, identifierades ytterligare 2 fall på en bekostnad av att genomföra 5 biopsier.

Cirka ett år efter diagnos och påbörjad behandling rapporterade 54% av barnen att de mådde bättre jämfört med innan diagnosen och cirka 70% följde en strikt glutenfri kost. Förändringen av barnens välbefinnande visade sig vara relaterad både till hälsoeffekter efter påbörjad behandling såväl som till sociala konsekvenser av att följa behandlingen. De med störst hälsovinster kunde vara de som led mest i form av sociala konsekvenserna och vice versa. Även om både barn och föräldrar beskrev förvåning och bestörtning när barnets celiaki upptäcktes så uttryckte de tacksamhet för att ha fått vetskap om sjukdomen. En majoritet tyckte att en allmän celiaki-screening skall införas i Sverige, men man föreslog att den i så fall skulle genomföras tidigare i livet och riktas mot barn i småbarns- eller förskoleåldern.

**Slutsatser**

Acknowledgements

I wish to thank all children, and their parents, that participated in the ETICS study. Especially I want to express my deepest gratitude to all screening-detected adolescents and parents who generously shared their experience of receiving the CD diagnosis with us.

This book is a product of research that has taken place during a long and important time period in my life. During this period we have also expanded our family and I have been involved in specialist training to become a clinical geneticist. There are many persons to thank for making this combination possible, and from the bottom of my heart I am grateful to all of you:

Västerbottens läns landsting, for making it possible to combine research with specialist training, and for encouraging medical doctors to conduct research. To my former bosses Roger Stenling and Göran Roos, and my current bosses Jens Boman and Göran Bergvall, for your positive attitude towards my involvement in research and most of all for always having a warm welcome when I have been away!

Anneli Ivarsson, my main supervisor. Our first meeting took place at Epi during the Christmas holidays where you passionately described your plans for the ETICS-study, and got me inspired. Since that day you have generously shared your knowledge concerning all aspects of research. Your support and challenges have encouraged me to develop into an independent researcher. Thank you for that!

Hans Stenlund, my co-supervisor, who with a calm and relaxed attitude has discussed statistical analyses and general aspects of (research) life with me.

Maria Emmelin, my co-supervisor, who with a friendly attitude has challenged me to embark on a journey to learn qualitative methodology. I have enjoyed our meetings and discussions. Although I was initially hesitant, just look where you got me! Now I try to help in your mission to be an eye-opener for other medical doctors regarding qualitative inquiries.
Olof Sandström, my co-supervisor, for taking the lead on the marker-paper when the time schedule changed, and for your support and encouragement during the work on this thesis.

Susanne Walther, my colleague, for smooth and friendly collaboration throughout the years.

Mariano Salazar, Lennarth Nyström and Torbjörn Lind, for valuable input to the thesis and the papers at the pre-defense seminar.

The "local" ETICS-group: Carina Lagerqvist, Anna Myléus, Katrina Nordyke, and Fredrik Norström, for all your cooperation over the years. Sometimes we have been confused, or even totally lost, often we have been overloaded with different work tasks, but we have always tried to solve the problems together.

The “national” ETICS-group: Annelie Carlsson, Lars Danielsson, Lars Stenhammar, for inventing and planning the ETICS-study together with Anneli, for making this thesis possible and for important feedback on my papers, and to Eva Karlsson for collaboration with the focus groups discussions. Also thanks to Lotta Webb and Lotta Högberg for making our meetings even nicer and more fun.

All the nice and friendly PreventCD researchers, including Luisa Mearin, who has inspired me with her way of leading the project and how well she has treated the young researchers who are involved. My thanks also to Caroline van den Esch for our collaboration with the PreventCD study design paper, and to Jihane Romanos and Cisca Wijmenga for collaboration on the genetic risk-model paper. Last, but not least, my thanks to Yvonne Wijkhuisen for making the periodic and annual scientific and management reports, including writing Form C and Cost-budget follow-up tables, a bit more fun than they actually are. We certainly learned a lot about formal reporting to EU along the way.

Ola Olén for your engagement in Paper 1 although it was summer.

Lars Weinehall and Nawi Ng, for inviting me to contribute to the development of the master course, Chronic Disease Epidemiology. Although it meant more work, I enjoyed every minute of working with both of you, and found it fruitful to do something other than working only with celiac disease.
Theme 2, Center for Global Health, under the leadership of Yulia Blomstedt and Lennarth Nyström, for arranging interesting sessions on how to evaluate complex interventions. They were of added value for my PhD studies.

All the nice people working at Epidemiology and Global Health for contributing to a friendly, fruitful and interesting work environment. I started to write a list of all of you, but then I got scared. What if I miss anyone? You know who you are, I don’t dare to mention you all by name in case I forget anyone!

The “boys” at Clinical Genetics, Göran Bergvall, Peter Nyberg, and Magnus Burstedt, for creating a fun and relaxed work environment during my research breaks. Also to Eva-Lena Stattin for encouraging me to continue with research even if it meant a longer period of absence from the clinic, and to Eva Holmberg for generously sharing your extensive clinical experience within the field of clinical genetics. I have missed you while working on this book.

The backbone of Clinical Genetics, with all competent and friendly medical laboratory scientists and to the clinical scientists, Jenni Jonasson, Kristina Cederqvist, Irina Gololeva, Björn-Anders Jonsson, and Anna Norberg, for your contribution to a nice work environment and for sharing your extensive knowledge on genetics with me. Thank you for remembering to invite me to after work also when I’m doing research. I look forward to working with you for many years.

My dear, wonderful, long-lasting friends: Helena Bäckström, Pernilla Christensen, Elin Enfält, Malin Eriksson, Sofi Gudmundsson-Öström, Jenni Jonasson, Maria Lidström, Anna Magnusson, Magdalena Marklund, Katrina Nordyke, Camilla Strindlund, Sussi Tegenborg, Taru Tervo, and Emma Thornéus, along with your partners and all your kids. Thank you for pleasant journeys, nice “girls’ nights”, endless chats on the phone and while walking around Holmsund or in other parts of the world. Thank you for traveling all across Europe to attend our Italian wedding. Thank you for letting me experience what true friendship really is.

To my parents, Tina and Olle Rosén, who have supported me throughout my life in all kinds of ways. Thank you for always having a warm welcome and for prioritizing your children and grandchildren.
To my little brother Lars and his wife Karin Rosén, for being who you are (like sisters (!) to me), and to my big brother Per Rosén, for your continuous Skype calls.

To my dear, clear-sighted grandfather, Lennart Rosén, who encourages me to work hard, but also to balance that by reminding me that what is of most importance, is the future generation. Thank you for always believing in me.

My deepest thanks go to Hans, for being the funniest, coolest and calmest husband imaginable, and to Hugo and Agnes for being the funniest, coolest and calmest kids imaginable. (They got that from both of us, however). Thank you for not being interested in this book but still letting me work (and monopolize our internet) whenever I needed to.

Hans, this autumn has been hard on both of us. You have taken full responsibility for the household including taking care of our children and me. Thank you for all your support. I couldn’t have done this without you.

“Mamma, är din bok klar den 13 november? Det kommer ut ett nytt dataspel då som jag vill spela online med mina kompisar och då behöver jag internet”
Hugo, 11 år

“Om det vore en tvärtomdag idag skulle mamma inte jobba med sin bok.”
Agnes, 6 år

“Vi har många tvärtomdagar att se fram emot hädanefter”
Författaren till denna avhandling

Funding
The thesis was funded by the County Council of Västerbotten, the European Union-supported project FP6-2005-FOOD-4B-36383-PREVENTCD, the Swedish Research Council, the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning, the Swedish Council for Working Life and Social Research, Svenska Celiakiförbundets Forskningsfond and Stiftelsen J.C. Kempes Stipendiefond. Thank you for making this research project possible.
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