CLINICAL SYMPTOMS, INTESTINAL HISTOLOGY AND NUTRIENT INTAKE: THE CELIAC STUDY IN EASTERN NORWAY (CELIEN)

MASTER THESIS OF TINE NYBRÅTEN TJØNSØ

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Clinical Symptoms, Intestinal Histology and Nutrient Intake:

The Celiac Study in Eastern Norway (CELIEN)

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Tine Nybråten Tjønsø, 2012
Executive Summary

**Background and Aims:** Little research has been conducted on the Norwegian celiac population. The clinical presentation of celiac disease (CD) is extensive, including both overt gastrointestinal complaints and vague atypical symptoms. Clinical symptoms and nutrient intake is an unexplored area, and may have great ramifications in terms of health and well-being. The impact of CD on celiac patients’ health and well being is of clinical importance to investigate. Considering that celiac patients receive financial support from the government, it is also of socioeconomic interest to gain more knowledge on this patient group. Hence, *The Celiac Disease Study in Eastern Norway* (CELIEN) was conducted. The main aim of this thesis was to investigate clinical symptoms and nutrient intake in the CELIEN study. Furthermore, clinical symptoms were explored in relation to intestinal histology, gluten-free diet (GFD) adherence and nutrient intake.

**Subjects and Methods:** The current study recruited 58 celiac patients (mean age 44 years; range, 20-71 years; 76% women), diagnosed at least 10 years ago. Data on clinical symptoms and GFD adherence was collected from questionnaires. Daily intake of micronutrients was calculated using a four-day weighed food record. Duodenal biopsy specimen and blood samples were collected to provide information on intestinal histology and serum micronutrient values. Anthropometric assessments served as additional indicators of nutritional status.

**Results:** The celiac patients in our sample reported only few and modest symptoms and health complaints. There was a significant difference in symptom score *Role-Physical* (SF-36), between the group with normal intestinal histology and the group with pathological features, with improved ability of working and accomplishing tasks in the group with normal histology. The adherent and non-adherent groups differed significantly on several symptom scales, with more symptoms reported in the non-adherent group. Furthermore, the results showed that the nutrient intake was not sufficiently covered regarding iron and dietary fibre in women, vitamin A and vitamin E in men and folate and vitamin D in both genders. The energy percentage from fat was above the recommended level in women. A more favourable intake of energy yielding nutrients was found in men. Higher percentage of energy from proteins and higher intake of calcium were associated with fewer symptoms.
Conclusions: Our sample comprised celiac patients in general good health in terms of reporting clinical symptoms and health complaints to a small extent. The relationship between GFD adherence and symptoms emphasize the importance of keeping a strict GFD. The suboptimal intake of folate, vitamin D and dietary fibre, in particular, and the unfavourable fat distribution, highlights the importance of improving the GFD.
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<td>Antigen Presenting Cells</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BMR</td>
<td>Basal Metabolic Rate</td>
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<td>CD</td>
<td>Celiac Disease</td>
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<td>CDAT</td>
<td>Celiac Disease Adherence Test</td>
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<td>CELIEN</td>
<td>Celiac Study in Eastern Norway</td>
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<td>CIA</td>
<td>Celiac Study in Agder</td>
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<td>CSI</td>
<td>Celiac Symptom Index</td>
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<td>GFD</td>
<td>Gluten-Free Diet</td>
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<td>GSRS-IBS</td>
<td>Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome</td>
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<tr>
<td>HDL-C</td>
<td>High Density Lipoprotein Cholesterol</td>
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<td>HLA</td>
<td>Human Leukocyte antigen</td>
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<td>IELs</td>
<td>Intraepithelial Lymphocytes</td>
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<td>IgA</td>
<td>Immune globulin A</td>
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<td>LDL-C</td>
<td>Low Density Lipoprotein Cholesterol</td>
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<td>MSS</td>
<td>Martine Symptom Score</td>
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<td>NCF</td>
<td>Norwegian Celiac Society</td>
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<td>NNR</td>
<td>Nordic Nutrition Recommendations</td>
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<td>OUS</td>
<td>Oslo University Hospital</td>
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<td>PAL</td>
<td>Physical Activity Level</td>
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<td>Subjective Health Complaints</td>
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<td>TG2</td>
<td>Tissue Transglutaminase</td>
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<td>WHO</td>
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1 Introduction

1.1 Background

Celiac disease (CD) can be defined as a chronic small intestinal immune-mediated enteropathy, precipitated by exposure to dietary gluten in genetically predisposed individuals [1]. The CD prevalence has increased during the recent years all over the world [2]. Until the late 1970s, the worldwide prevalence was estimated to be as low as 0.03%, whereas today the prevalence is estimated to be 1%. Increased awareness and improved diagnostic tools can probably explain some of the growing prevalence - but not all - it is likely that there is also a true increase in individuals getting CD. In Finland, the prevalence seems to have almost doubled during the last twenty years, from 1.05% in the end of the 80’s to 1.99% in the beginning of the 21st century. Lohi et al. found that this increase cannot be attributed to the improved diagnostics alone, but may be explained by environmental factors [2]. In Norway, the current estimated prevalence of CD is 1% [3].

Exclusion of food and beverages containing gluten is currently the only treatment for CD. There is evidence that untreated CD increases morbidity and mortality and impairs quality of life [4-6]. Adherence to a strict gluten-free diet (GFD) will in most cases lead to remission of symptoms, normalisation of the duodenal mucosa, a decline in morbidity and mortality and improved psychological well-being [7-10]. The fact that untreated CD is associated with health complaints, impaired quality of life and increased morbidity and mortality, makes it important to pay attention to this patient group.

The Norwegian celiac population has been scantily investigated. As a result, there is lack of data on clinical symptoms in this patient group: symptom prevalence and what mode of presentation involves for individuals with CD regarding nutrient intake, nutritional status and quality of life. GFD adherence in the celiac population in Norway is only sporadically studied. However, the *Celiac Study in Agder (CIA)* was initiated in 2010 and is ongoing. CIA investigates the impact of living with CD in terms of GFD adherence, quality of life and nutrient deficiencies. This work will provide valuable knowledge to the research field.

What currently is acknowledged is that GFD adherence is insufficient in several European countries [11]. Avoidance of health complaints and clinical symptoms may be an incentive for keeping a strict GFD. However, a U.S study conducted by Leffler et al. found no difference in
GFD adherence between patients presenting with *classic* symptoms e.g. diarrhoea, abdominal pain and weight loss as opposed to those who were *asymptomatic* or had more subtle symptoms as anaemia, constipation, and osteopenia [12]. This is supported by findings from two studies conducted in Finland [7, 13]. In another study by Leffler et al., improved GFD adherence was found among CD patients with few symptoms [14].

A study from Finland found that CD patients improved in terms of gastrointestinal symptoms and well-being after starting a GFD and achieved levels equal to healthy controls [7]. Contrary to this, a Swedish study found that even after several years on a GFD, celiac patients did not achieve similar subjective health status as reported by the general population [15].

At present, a definite relation between intestinal histology and symptom impact has not been established. A study conducted by Brar et al. found no association between mucosal damage and clinical presentation [16]. This is in agreement with findings from a study by Murray et al. [17]. Despite of clinical improvement on a GFD, histological abnormalities may persist [18]. On the other hand, examination during endoscopy found that patients presenting with the classical form of CD showed more severe damage than subclinical patients [19]. Noteworthy, histological lesions are not specific to CD [20]. The differential diagnoses include small intestinal bacterial overgrowth, intestinal T-cell lymphoma, irritable bowel syndrome, refractory CD, microscopic colitis and disaccharide intolerance. This, of course, complicates the clinical picture [21].

In terms of nutritional outcomes, it seems likely that both mucosal alterations and clinical symptoms are able to impair nutritional status. Serum ferritin, transferrin and erythrocyte folate levels were found to be lower in patients with total villous atrophy compared to patients with partial and subtotal atrophy [22]. Gastrointestinal symptoms may impair appetite, which can lead to a poor nutrient intake. Lack of a clear correlation between clinical presentation and mucosal damage may imply that asymptomatic as well as symptomatic CD patients may be suffering from nutritional inadequacy.

In addition to its clinical importance, the study is of socioeconomic interest because celiac patients receive financial support from the Norwegian government for expensive diet. *The Celiac Study in Eastern Norway* (CELIEN) was therefore initiated and provides the frame for this master thesis.
1.2 Celiac Disease (CD)

1.2.1 Pathogenesis

Ingestion of gluten and analogues from wheat, barley and rye will in CD trigger an immune response, which leads to hyperplasia of the enterocytes, intestinal atrophy and mucosal infiltration of lymphocytes [23]. Persistent exposure to gluten can result in malabsorption and consequential nutrient deficiencies. This can lead to development of bone disease, neurological disorders, iron anaemia and other haematological manifestations as a consequence of folate and B₁₂ deficiencies [24]. CD involves an increased risk of developing T-cell lymphoma [4].

CD is considered an autoimmune, genetically conditioned disease, triggered by an environmental factor, the gliadin and glutenin peptides in gluten [25]. The gluten peptides trigger the immunological reactions, which cause rising levels of certain antibodies and other inflammatory agents in addition to the development of structural changes in the small bowel mucosa. Although the inflammation is induced by the foreign protein, gluten, CD is regarded an autoimmune disease because of the crucial role of auto antibodies to tissue transglutaminase (TG2) in the disease process.

Gluten is poorly digested, and will after ingestion reach the intestinal lumen as large polypeptides [26]. In individuals with CD, gluten peptides pass through the jejunal wall into the submucosa (Figure 1). The gluten peptides become target for the intracellular enzyme, TG2, which deamidates the peptides and enhances their affinity to human leukocyte antigens (HLAs) possessing DQ-2 or DQ-8 molecules. CD4-positive T-cells recognize the gluten epitope when attached to HLAs on the cell surface of antigen presenting cells (APCs). This result in T-cells producing cytokines, which contribute to the inflammatory process that induce villous atrophy. The gluten peptides activate both the innate and the adaptive immune system.
1.2.2 Clinical Manifestations

CD can be difficult to diagnose because of its wide range of manifestations. The clinical presentation can be subtle. CD is associated with classic gastrointestinal complaints as well as atypical symptoms [9]. The classical presentation is primarily characterized by diarrhoea, malabsorption and weight loss [9]. Frequently, individuals with CD do not manifest with gastrointestinal symptoms [28]. Tiredness, unexplained weight loss, stomach and intestinal distress, growth restrictions, enamel defects, bone and joint complaints, depression, oedema, infertility and neuropsychological and somatically complaints are a variety of signs that can be observed in CD [29-32].

Studies suggest that the clinical presentation of CD has changed during the recent years as a growing proportion of celiac patients now present with atypical symptoms [28]. It has been
proposed that roughly 50% of individuals with CD are either asymptomatic or have nonspecific symptoms [33] [34]. There has been a significant decline in the proportion of patients presenting with diarrhoea. In patients diagnosed before 1981, 91.3% were presenting with diarrhoea, whilst only 37.2% of the patients diagnosed after the millennium had diarrhoea [35]. Hovdenak et al. conducted a study among Norwegian blood donors and found that 1 in 340 had asymptomatic CD, and that in spite of apparently being healthy could be suffering from secondary deficiency diseases [36].

The way CD appears in the celiac population is commonly illustrated as an iceberg (Figure 2). Only a small fraction of the celiac population are presenting with overt clinical disease, representing the tip of the iceberg. A substantial proportion of CD cases is subclinical and is illustrated by what is hidden under the water.

![Figure 2. The Celiac disease iceberg. Reproduced from Feighery [37]](image)

Use of improved diagnostic tools makes it possible to identify celiac patients despite vague and non-specific clinical presentation. This has given rise to the following classification of CD: The classical CD is characterized by villous atrophy and malabsorption with gastrointestinal symptoms such as diarrhoea, bloating and weight loss or other signs of nutrient deficiencies. Atypical CD differs from the classical type in that it may only display minor or total absent of gastrointestinal complaints, but still involving mucosal changes and
celiac specific serology. *Asymptomatic* or *silent CD* is described with no clinical signs indicating CD, but with an abnormal mucosal architecture and positive serology. *Latent CD* involves absence of symptoms, normal histology, but which subsequently develops into CD. *Latent* CD may also refer to earlier CD patients whose mucosa retains normal despite of gluten ingestion [38]. All of these phenotypes represent individuals who are genetically predisposed to CD.

Mustalathi et al. revealed that even screening-detected celiac patients, both symptomatic and asymptomatic patients, showed an improvement in gastrointestinal symptoms and quality of life after initiating a GFD [7]. Collin et al. have been evaluating the question of population screening of CD. Based on their review, it appears that follow-up of symptomatic CD patients should be prioritized, since these individuals seem to be the most vulnerable to complications of CD [39].

### 1.2.3 Diagnostics

The severity of the intestinal lesion can range from inflammatory cells infiltrating the epithelium and lamina propria, but with otherwise normal mucosal architecture, to crypt hyperplasia and varying degree of villous atrophy and to a completely destructed mucosa. Intestinal lesion severity are usually graded according to the Marsh-Oberhuber classification [20].

The current guidelines state that a definite CD diagnosis has to be established on results from duodenal biopsies: detection of villous atrophy with crypt hyperplasia and intraepithelial lymphocytosis when exposed to dietary gluten [40]. According to the diagnostic criteria, clinical improvement should be apparent after initiating the GFD. If an individual has started the GFD before getting a diagnosis, it will be necessary to complete a gluten challenge before serology and histology testing. In Norway the gluten challenge lasts two to four weeks before repeated serology and duodenal biopsy

Detection of immune globulin A (IgA)-antibodies to TG2 supports the diagnosis and is used initially, when CD is suspected but not confirmed. In a systematic review the specificity and sensitivity was found to be >98 % and >93%, respectively [41]. Detection of IgA-antibodies

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1 Practice among gastroenterologists and dieticians at OUS, Rikshospitalet.
to gluten is no longer considered an important diagnostic tool because of poor sensitivity and specificity [42].

Celiac patients may have antibodies to a component in the tissue of smooth muscle cells called endomysium. This test has high specificity and sensitivity (>99% and >93% respectively) [41]. The anti-TG2 test is though easier to perform than the antiendomysial test [39].

HLA-typing for HLA-DQ2 and HLA-DQ8 is a part of the diagnostic assessment. About 50% of the overall population has HLA consistent with CD, which implies a poor specificity. Though, a negative test is useful to rule out CD. The positive predictive value is calculated to 6% in contrast to the high negative predictive value showing 97% [43].

### 1.2.4 Dietary Treatment

The GFD involves complete avoidance of the gluten containing wheat, rye and barley. In addition, foods and beverages containing gluten, or contaminated with gluten must be excluded from the diet. Hidden gluten sources can be found in dietary supplements, pharmacological products and cosmetics and may lead to unintentional gluten exposure [44, 45].

Lactose intolerance may appear secondary to CD [46]. Before the small bowel has time to recover after initiating the GFD, it can be advisable to reduce the intake of dairy products containing lactose [3]. These products should be reintroduced when the intestine has normalized, as they are important sources of calcium and other micronutrients.

Due to chronic malabsorption, vitamin and mineral supplementation may be required temporarily, after initiating the GFD [3]. The duodenum is often more damaged than the rest of the small intestine in untreated CD. Hence, these patients are particularly vulnerable of developing deficiencies of iron, folate, vitamin D, selenium, and calcium as duodenum is their site of absorption [47] [48].

Histological recovery after initiating a GFD takes time, and was absent or incomplete in a subgroup of patients according to Wahab et al. [49]. Within two years, only 65% of the patients in their study reached histological remission. Within five years 85.3% was in remission. Recovery time was found to differ in children and adults, a larger proportion of
children recovered compared to adults. Another study concluded that abnormal endoscopic
and histopathological appearance persisted in spite of clinical improvement [18]. In terms of
clinical response to treatment, celiac patients seem to improve rapidly after initiating a GFD.
A cohort study found that the mean resolution time was four weeks [9].

The advisory council of the Norwegian Celiac Society (NCF) has made guidelines for follow-
up of patients with CD [3]. These guidelines propose that celiac patients should be controlled
three and 12 months after initiating the GFD with regard to the dietary treatment,
anthropometric measurements, clinical status and blood samples, if necessary. After 12
months an antibody test should be done and where there is doubt about diagnosis (e.g. little
effect from the GFD), a new duodenal biopsy should be conducted. The patient should be
examined every 2nd year thereafter. The practice is highly variable and experience shows that
most celiac patients do not get this follow up from the health system in Norway.

Celiac patients are a heterogeneous group [50]. Some individuals show mucosal alterations
after ingestion of only small amounts of gluten while others are more resistant [51]. The
clinical response to gluten, in terms of symptoms, differs likewise [52]. Sensitive celiac
patients choose to keep their diet free from wheat starch even though wheat starch is accepted
in the GFD according to the Norwegian guidelines [3].

On January 1st 2012, the labelling guidelines of gluten-free products in Norway were
modified [53]. The current guidelines state that products, labelled gluten-free can contain up
to a maximum of 20 mg gluten per kg, and products labelled very low in gluten, can contain
up to a maximum of 100 mg per kg. As a result, CD patients sensitive to wheat starch cannot
just look for products naturally free from gluten, as earlier, but must read the ingredients list.

Inclusion of oats in the GFD has been questioned, both in the context of contamination and
the findings that suggest that some celiac patients can be intolerant to the avenin component
in oats [54]. The Norwegian researchers Guttormsen et al. concluded from their work that oats
can be tolerated in most adult celiac patients [55]. The oat production in Norway is rigidly
controlled, and oats can be considered safe in terms of contamination [54]. The new
guidelines state that pure oats can be included in the GFD.
1.2.5 Gluten-free Diet (GFD) Adherence

Adherence to a GFD can be difficult in various ways. In terms of managing avoidance of gluten per se, but also considering participation in social life can be a challenge [56]. Gluten is ubiquitous in pre-packed food items [57], and may be difficult to discover. Another aspect is the cost of gluten-free food items. Gluten-free food items are much more expensive than the equivalent gluten-containing foods [58]. This can be an additional constraint in following a GFD. Gluten contamination is also an obstacle to GFD adherence, and is an issue both in the milling industry and at household level [59, 60].

A systematic review found that the factors of greatest impact for GFD adherence were cognitive, sociocultural and emotional influences in addition to regular dietetic follow-up and membership of an advocacy group [11]. In 1989, a small study was conducted on GFD adherence in celiac patients in Norway [61]. Gluten-free diet adherence was assessed by a self-administered questionnaire. The study found that half of the 28 participants with CD ate food that was not sure to be gluten-free. Among the adults, 22% did not adhere consistently to a strict GFD. Practical and social problems were reported in relation to the GFD.

In order to investigate adherence to GFD, proper tools or methods are required. No standard objective method currently exists, however, several methods have been used in studies exploring adherence to a GFD, such as: questionnaires, food records, 24h-recall, clinical interviews, serology, biopsy, and self-reports [11]. Leffler et al. propose that a standardized assessment of GFD adherence by an expert nutritionist is the best method [21]. Histological findings as an indicator of adherence have not been convincing, as there are only weak correlations of histopathological findings with clinical presentation or assessed GFD adherence [18, 62]. Nevertheless, biopsy is considered the gold standard when measuring disease activity. Leffler et al. and Biagi et al. recently developed tools which enable an evaluation of GFD adherence in a more standardized fashion [63, 64]. Celiac Dietary Adherence Test (CDAT) is developed by the former and has been shown to correlate with a standardized dietician evaluation of GFD adherence and IgA-TG2 titers [63]. The test is easy to administer and is suitable for use in the clinic.

1.2.6 Clinical Symptoms and GFD Adherence

Intuitively one might think that asymptomatic individuals are more apt to dietary transgression than individuals who are sensitive to very small amounts of gluten. This is in
agreement with findings from an Irish 28-year follow-up, where the most important motivating factor for dietary adherence was avoidance of symptoms [65].

Ciacci et al. investigated GFD adherence, assessed by a clinical interview, and intestinal damage in adults with CD [62]. Based on an observed negative correlation between adherence and baseline haemoglobin status, they concluded that GFD adherence was better in individuals who experienced more severe symptoms before treatment.

In exploring symptoms in association with GFD adherence, it is important to be aware of the double implication of symptom severity. As suggested by Ciacci et al., symptom relief can be a reason for adhering strictly to the GFD [62]. On the other hand, if symptoms rarely appear despite of gluten ingestion, GFD adherence may probably be poorer. Symptoms alone are not a good predictor of GFD adherence and must be considered together with other factors.

1.2.7 Nutritional Implications

Dietary restrictions are required in the treatment of various food hypersensitivity diseases. This may have implications for nutritional status and health. Diseases that necessitate exclusion of most of or a whole group of food have an increased potential of causing nutritional deficiencies. The greatest impact of the GFD on the dietary intake may be exclusion of regular grain products. This can cause an inadequate intake of nutrients where grain products are the most significant source. In Norkost 1997, bread and grain products contributed to 42% of the total carbohydrate intake [66] The proportion of energy contribution from fat, carbohydrates and proteins may be disturbed on a GFD, as food rich in carbohydrates often contains gluten and consequently are avoided. Bardella et al. found that celiac patients who followed a strict GFD had a lower intake of total energy and a larger contribution of energy from fat and less from carbohydrates, compared to controls [67]. A study that investigated children on a GFD also found a pattern of increased consumption of fat compared with healthy controls [68]. Gluten-free food items may be used as substitution for the equivalent gluten-containing foods. However, studies where the nutritional quality of gluten-free products has been analyzed show that gluten-free products may not be as nutritious as the equivalent gluten-containing products [69] [70]. Gluten-free flours and baking mixes usually consist of refined flours and have a greater content of starch, poor in vitamins and minerals and smaller amounts of fibre than ordinary flour [70]. A Swedish study found that celiac patients had an insufficient vitamin status compared to the general
population [71]. Adequate intake of fibre and micronutrients may therefore require an extra effort by celiac patients.

The Norwegian health authorities conduct surveys to obtain knowledge about the nutrient intake in the population and data on how the Norwegian diet is changing. The 2011 report revealed that the Norwegian diet was adequate regarding most nutrients, but that the mean daily intake of dietary fibre, vitamin D, vitamin E, calcium and folate did not reach recommended levels [72]. Additionally, women of reproductive age had an inadequate intake of iron.

Other key results from the report show that the energy proportion from fat has in recent years increased to 37E%, protein constitutes about 14E% and carbohydrates approximately 50E%. The content of saturated fatty acids, sugar and salt in the Norwegian diet is above the recommended level while the intake of dietary fibre, vitamin D and folate is below the recommendations [72]. Saturated fatty acids constitute approximately 15-16% of the total energy intake and should be kept below 10E%. The dietary content of polyunsaturated fatty acids has increased from 6 to 7E% the last decade while monounsaturated fatty acids has decreased and the content of trans fatty acids has reached recommended levels (<1E%). The average sugar intake is above the reference level (<10E%) as well. Intake of dietary fibre is 16-19 g per person per day, which is insufficient according to the Nordic Nutrition Recommendations (NNR) [73]. The recommendations regarding energy providing nutrients are summarized in Table 1.

**Table 1.** Recommended\(^a\) intake of energy providing nutrients as percentage of total energy intake (E%).

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Reference level (E%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>25-35</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>10-15</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>5-10</td>
</tr>
<tr>
<td>Omega-3</td>
<td>~1</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Proteins</td>
<td>10-20</td>
</tr>
<tr>
<td>Carbohydrates(^b)</td>
<td>50-60</td>
</tr>
<tr>
<td>Sugar</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Dietary fibre</td>
<td>25-35 g/day</td>
</tr>
</tbody>
</table>

\(^a\)Nordic Nutrition Recommendations 2004

\(^b\)Carbohydrates including dietary fibre
Some studies have questioned the nutritional adequacy of celiac patient’s diet, suggesting lower nutritional value of the gluten-free food items and the challenge of managing a restricted diet as reasons for this [67, 71, 74]. It can be hypothesized that the abovementioned nutrients, which are inadequately covered in the overall Norwegian population, could be particularly difficult to cover for celiac patients.

Besides being the most important contributor of energy, bread and grain products are the major source of carbohydrates, iron and fibre in the diet according to the Norkost 1997 [66]. Grain products are also a significant source of proteins and several vitamins [75]. Given that these products are excluded from a GFD, it is of great interest to investigate celiac patient’s diet. Alvarez-Jubete et al. emphasized the potential of improving the nutritional value of gluten-free breads by using pseudo cereals as amaranth, quinoa and buckwheat [74]. Additionally, oats is a valuable source of fibre in the diet and can make the food more palatable. Oats has been shown to improve the nutritional value of the GFD [76].

1.2.8 Nutritional Status

An adequate nutritional status can be defined as a condition of sufficient supply of energy and nutrients through diet, to keep the composition and function of an individual within the normal range [77]. An insufficient dietary intake will result in degradation of body tissue, which consequently leads to weight loss. Children are particularly vulnerable in this respect, considering increased requirements to support growth and development. It has been suggested shorter adult height in men with delayed CD diagnosis [78].

In classic CD, weight loss and nutrient deficiencies, secondly to diarrhea and malabsorption, will impair nutritional status. A study from U.K found that celiac patients with body mass index (BMI) less than 20 had significantly lower levels of hemoglobin and were more likely to manifest diarrhea [79]. Additionally, low BMI was related to a higher prevalence of severe intestinal lesions. A higher amount of the patients were described as being overweight than underweight, but the majority was of normal weight. The greater prevalence of overweight patients with less typical symptoms are in consistency with the trend toward a CD presentation increasingly dominated by atypical symptoms as suggested by Rampertab et al.[35].
A recently conducted nationwide study in Finland found that BMI improved on a GFD [80]. The overweight and obese patients lost weight while the underweight gained weight. Another study described weight gain in overweight individuals after initiating the GFD [79]. A significant lower BMI among treated CD patients compared to aged matched healthy controls has been described in a Danish study [81].
2 Objectives

The main aim of this master thesis was to investigate clinical symptoms and nutrient intake in adult celiac patients of Eastern Norway. Moreover, the aim was to study clinical symptoms in relation to intestinal histological findings and GFD adherence.

The following specific objectives were formed:

1) To study clinical symptoms in a sample of Norwegian celiac patients.
2) To study the association between clinical symptoms and intestinal histology.
3) To study the association between clinical symptoms and GFD adherence.
4) To study nutrient intake in relation to the Nordic Nutritional Recommendations.
5) To study the association between clinical symptoms and nutrient intake.
6) To study the association between intestinal histology and nutritional status.
3 Subjects and methods

3.1 Sample size

The level of significance is 0.05. With an expected withdrawal of 15%, we aimed at recruiting 80 individuals to obtain data from 68 subjects, divided into two groups. With a 90% power, we could expect to detect a difference of 0.8 between the two groups.

3.2 Recruitment

CELIEN had a target population comprising adult celiac patients from Eastern Norway. Inclusion criteria were: age >18 years old, inhabitant of Eastern Norway, verified CD based on duodenal biopsy and the individuals should have been diagnosed with the disease at least 10 years prior to the study. Exclusion criteria were: individuals from other areas than Eastern Norway, individuals on steroids or anti-inflammatory drugs, transplant patients, individuals with complications due to diabetes or individuals that for any reason were incapable of cooperating. Individuals who already participated in focus groups and in pilot study were excluded from taking part in the main study.

Participants in the project were mainly recruited through NCF, the largest advocacy group for celiac patients in Norway. An announcement with information about the project was published on NCF’s website: the main website, the website for adolescence and the corresponding Facebook groups. See Appendix1. A written text in glutenFRI (formerly Cøliaki-nytt), a magazine for the members of NCF, as well as newsletters from some of the locale support groups also contributed to the recruitment process.

3.3 Study Conduct

Before the first visit at Oslo University Hospital (OUS), Rikshospitalet, the participants received the symptom specific questionnaires per mail, in addition to written information and a consent form. They were asked to complete the questionnaires prior to the first meeting. Study conduct is illustrated in Figure 3.

At the first visit, a dietician collected the completed questionnaires and checked that each item was answered. A additionally symptom specific questionnaire, Celiac Symptom Index (CSI),
was completed and the participants received a kitchen scale and were given instructions on how to carry out a four-day weighed food record.

Measures of height, weight, and waist and hip circumference were recorded. Blood samples were collected and gastroscopy with biopsy was performed subsequent to the consultation with the dietician.

At the second visit, the participants returned the four-day weighed food record to be checked by the dietician.

**Figure 3.** Study conduct of CELIEN
4 Methods for Measuring Clinical Symptoms

A set of different questionnaires were used to measure clinical symptoms and health complaints; Martine Symptom Score (MSS, Martine questionnaire), CSI, Subjective Health Form (SHC), Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome (GSRS-IBS) and Short Form-36 (SF-36).

To simplify, an expanded definition of the term clinical symptoms has been used in the current thesis, including both physical and psychological health complaints.

Since there is no standard method for measuring adherence of GFD adapted for celiac patients in Norway, the Martine questionnaire was developed especially for this study. Only the symptom specific items in Martine are included in this thesis. Items on GFD adherence are studied in another master thesis [82].

4.1 The Martine Questionnaire and the Martine Symptom Score (MSS)

The Martine questionnaire was developed on the basis of knowledge from literature reviews and focus groups with celiac patients. Pilot testing were conducted several times and repeated reviews were done by experienced dieticians before questionnaire completion. The questionnaire has been validated against intestinal histology in another master thesis [82]. The process of developing the Martine questionnaire is described in detail in Appendix 2.

The Martine questionnaire is divided in three sections, see Appendix 3. The first section concerns demographic data, sample characteristics and items related to transgression from the GFD. The second section has questions concerning adherence to the GFD and includes the symptom specific items that were examined in this thesis. The last section has a qualitative approach with items related to barriers to GFD adherence.

The four items linked to symptoms were included in the current thesis:
Item 13: Symptoms experienced during the last 4 weeks: Weight change, breaking wind, constipation, diarrhoea, fatigue, headache, abdominal pain, bloating, nausea, vomiting, other symptoms, (yes, no).

Item 14: How often do you experience symptoms? (Daily, weekly, monthly, a few times per year, never).

Item 15: If you have ingested gluten, do you experience symptoms? (Always, often, sometimes, rarely, never).

Item 16: How frequently do you get symptoms, if you ingest even tiny amounts of gluten, e.g. bread crumbs? (Always, often, sometimes, rarely, never).

MSS was derived from question 13. The score is calculated by adding the eleven responses (no=0, yes=1), i.e. The minimum score was 0, and the maximum score was 11. Higher scores indicate more symptoms.

4.2 Celiac Symptom Index (CSI)

CSI is a validated tool to assess disease-specific symptoms in celiac patients [14]. It consists of 16 questions, which can be divided into two domains: 1) 11 questions about CD-related symptoms and 2) five questions concerning general health and CD related health. Each question has five possible response categories. CSI is scored by adding responses from each question. The minimum symptom score is 16 and maximum is 80. Higher scores indicate more severe symptoms and have been found to correlate with poor quality of life and lower GFD adherence[14]. Leffler et al. found that scores of 30 or less were associated with excellent GFD adherence, while scores of 45 or greater were related to lower GFD adherence. Apart from this a cut-off value has not been established. The questionnaire is completed by self-administration. CSI was translated to Norwegian by Gry Skodje (dietician at OUS Rikshospitalet) according to the back-translation procedure [83]. The authors approved the translation. See Appendix 4.
4.3 Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome (GSRS-IBS)

GSRS-IBS is a valid and reliable symptom scale developed for patients with IBS [84]. It includes symptoms related to irritable bowel syndrome and is an expansion of the validated Gastrointestinal Symptom Rating Scale, GSRS, which has been widely used in celiac patients [7, 13, 85]. GSRS-IBS detects which specific symptoms that are the most troublesome, and monitors how symptoms respond to treatment. A cut-off for the presence of IBS has not been established. GSRS-IBS consists of 13 items, categorised into five clusters of symptoms: abdominal pain, bloating, diarrhoea, constipation and satiety. It measures symptoms during the past 7 days with a 7-point Likert scale (no discomfort to very severe discomfort). Each item provides a score from 1 to 7 and the total score is calculated by adding each item’s separate score. Minimum sum score is 13, and maximum is 91, with higher scores denoting more symptoms. GSRS-IBS is usually performed on two different occasions, measuring how symptoms respond to treatment.

The test is self-administered. Brottveit et al. adjusted the GSRS-IBS before use in a study on patients with possible gluten intolerance [86]. They used 3 days instead of 7. The altered version used in this study has not been validated in a celiac population, but is widely used in CD patients and patients with gluten intolerance without CD at OUS, Rikshospitalet. See Appendix 5.

4.4 Subjective Health Complaints (SHC)

The self-administered SHC intends to record subjective health complaints, regardless of any particular diagnosis [87]. The original form consists of 29 questions concerning severity and duration of subjective somatic and psychological complaints. The severity of each complaint is graded 0 = none, 1= some, 2= much and 3= severe. The complaints are categorized into five categories: Musculoskeletal pain, pseudoneurology, gastrointestinal problems, allergy and flu. The sum score ranges from 0-87 and is calculated by adding the degree of severity for each question in each category. The version of SHC that was used in this study has been modified by Brottveit et al. in terms of duration of reported complaints. The participants were asked to record subjective health complaints experienced during the last 3 days instead of 30 days as in standard SHC. This change is not validated in Norway, but is widely used in CD
patients and patients with gluten intolerance without CD at OUS, Rikshospitalet. See Appendix 6.

4.5 Short Form-36 (SF-36)

SF-36 is a 36-item multi-purpose, generic health survey, which records different aspects of self-perceived health; well-being and functional health [88]. The questionnaire consists of 8 scales: Physical Functioning concerns with functioning in daily activities. Role-Physical deals with ability of working and accomplishing tasks. Bodily Pain measures pain, in general, and records how bodily pain affects work. General Health deals with the subjective understanding of health and own health compared to others. Vitality concerns with mentally and bodily vitality. Social Functioning deals with mental and physical health and how it affects social life. Role-Emotional concerns with how emotions affect work and accomplishing tasks. Mental Health deals with nervousness, happiness and sadness. The version of SF-36, which was applied in this study, had an additional scale: Change in Health. This version was used in a study conducted by Loge and Kaasa, which provides normative data from the general Norwegian population [89]. This item records current health compared to earlier. See Appendix 7.

The scales in SF-36 are scored separately and each item is used in scoring only one scale. The eight scales are scored from 0-100, where lower scores indicate poorer health on the particular health aspect. The scale Change in health is scored from 1-5, higher scores indicating deterioration in health. SF-36 has been translated to Norwegian and is validated in Norway [90, 91].

4.6 Four Day Weighed Food Record

Weighed food record is a widely used method. It is often referred to as the "gold standard" as it give the most precise quantitative measurement of intake [92]. The method is considered to provide sufficient data when the purpose of a study only requires mean values and distribution of consumption of a group and, was therefore chosen for this study [93]. This method is described in detail elsewhere [94, 95].

The participants were asked to weigh and record all foods and beverages, including supplements, consumed on four consecutive days. The subjects recorded the corresponding
brand names, type of preparation and recipes for home cooked dishes. Tuesday to Friday was chosen to include a part of the weekend. Additionally, the purpose of the weighed food recording and the importance that the participants kept with their regular food habits during the registration period was emphasized.

The participants received a kitchen scale (OBH Nordica electronic kitchen scale type 9851), and a food diary with a short written instruction. See Appendix 8. The kitchen scale measures from 5 g to 5 kg with an interval of 1 gram and with an accuracy of ±1%. The kitchen scales were calibrated and had never been used.

**Validity of four day weighed food record**

Under-reporting of dietary intake was determined by a commonly used method developed by Goldberg et al. [96] Mean energy intake and mean basal metabolic rate (BMR) for the study sample allowed us to estimate the expected physical activity level (PAL), with the assumption that the subjects were in energy balance. Degree of under-reporting at group level was calculated by comparing the estimated PAL (mean energy intake /mean BMR) with PAL from Goldberg’s equation.

### 4.7 Celiac Dietary Adherence Test (CDAT)

CDAT is a 7-item instrument developed for assessing GFD adherence in a standardized way when monitoring treatment response [63]. The items deal with issues which both implicitly and explicitly measure GFD adherence. A couple of items are related to self-perception and personality trait. The test is self-administered. Each item is recorded by a 5-point Likert scale. The sum score ranges from 13-35 and is calculated by adding the response from each item. Higher score indicates worse adherence (score< 13= adequate adherence, score ≥13 = inadequate adherence). The instrument was developed and validated in American celiac patients. Celiac Dietary Adherence Test was translated to Norwegian by Gry Skodje (dietician at OUS, Rikshospitalet) according to the back-translation procedure[83]. The authors approved the translation. See Appendix 9.

The test score from CDAT was chosen as a measure of GFD adherence since it has been shown to reach sufficient specificity and sensitivity to measure GFD adherence when compared to other methods as IgA-TG2 assessments and GFD adherence evaluation by a
dietician[63]. However, the Norwegian version was not validated before use in the current study [82].

4.8 Nutritional Status

4.8.1 Anthropometry

Height, weight and waist and hip circumference were recorded. Electronic devices were used for the height (cm) and weight (kg) assessments (Seca 772021 electronic scale and Seca 242 fixed electronic measuring rod, Vogel & Halke GMBH & CO, respectively). Body mass index (BMI) was calculated as weight divided by height$^2$ (kg/m$^2$). Height and weight was measured fully dressed, but without shoes and outdoor clothing.

A flexible tape measure was used to assess waist and hip circumference. Waist circumference (cm) was measured directly on the skin, while hip circumference (cm) was measured with clothes. The procedure of assessing hip and waist circumference was done according to guidelines of the World Health Organization (WHO) [97]. The equipment used for the anthropometric measurements were calibrated.

4.8.2 Nutritional Biochemistry

Fasting blood samples were obtained prior to the gastroscopy at the first hospital visit at OUS, Rikshospitalet.

A blood sample: iron, haemoglobin, ferritin, transferrin, transferrin saturation, folate, vitamin B$_{12}$, homocysteine, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, calcium, albumin adjusted calcium, sodium, potassium, phosphate, and zinc were conducted and analysed at the Department of Medical Biochemistry at OUS, Rikshospitalet. The vitamin D metabolites, 25-hydroxy vitamin D and 1,25- dihydroxy vitamin D, thiamine and vitamin B$_6$, were measured at the Hormone Laboratory, OUS, Aker. Selenium was measured at OUS, Ullevål.

4.9 Gastroscopy

Small bowel biopsies were obtained in accordance to the procedure described by Brottveit et al. [98] A minimum of four duodenal biopsies was obtained from each participant.
Pathologists at OUS, Rikshospitalet conducted the morphological examination and evaluated the biopsies. The morphological features of the specimen were graded according to the Marsh classification as modified by Oberhuber [20] (Table 2), although at OUS, Rikshospitalet the diagnostics is based on an intraepithelial lymphocyte count < 30 and > 30. The classification range from 0 to 3, where higher Marsh-Oberhuber grade indicates increasing degree of intestinal destruction (grade 0 indicates normal mucosa while grade 3 means complete villous atrophy).

**Table 2. Marsh-Oberhuber scoring classification [20]**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histological description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh, grade 0:</td>
<td>&lt; 40 IELs(^{a}) per 100 enterocytes, normal crypts and villi.</td>
<td>Normal histology</td>
</tr>
<tr>
<td>Marsh, grade 1:</td>
<td>&gt; 40 IELs(^{a}) per 100 enterocytes, normal crypts and villi.</td>
<td>Not diagnostic of CD. Early or mild CD. Can be seen in healthy individuals. Bacterial overgrowth, helicobacter pylori, irritable bowel syndrome etc. [20]</td>
</tr>
<tr>
<td>Marsh grade 2:</td>
<td>&gt; 40 IELs(^{a}) per 100 enterocytes, crypt hyperplasia and <em>normal</em> villi.</td>
<td>Non-specific.</td>
</tr>
<tr>
<td>Marsh, grade 3a:</td>
<td>&gt; 40 IELs(^{a}) per 100 enterocytes, crypt hyperplasia and <em>mild</em> villous atrophy.</td>
<td></td>
</tr>
<tr>
<td>Marsh, grade 3b:</td>
<td>&gt; 40 IELs(^{a}) per 100 enterocytes, crypt hyperplasia and <em>moderate</em> villous atrophy.</td>
<td></td>
</tr>
<tr>
<td>Marsh, grade 3c:</td>
<td>&gt; 40 IELs(^{a}) per 100 enterocytes, crypt hyperplasia and <em>total</em> villous atrophy.</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)IELs, intraepithelial lymphocytes
4.10 Data analysis

Nutrient intake was calculated from the four day weighed food records with the software Mat på Data version 5.1. Statistical analysis was performed using SPSS Statistics version 19.0.0. The significance level is 5%.

Where two groups were compared regarding a normal distributed continuous variable, an independent-samples t-test was performed. When the continuous data were not normally distributed, a Mann-Whitney U test was used. Categorical data are described by counts and percentages. Normally distributed data are presented as means and standard deviations (SD) while data not normally distributed are presented as medians and quartiles (25th and 75th percentiles: Q₁ and Q₃).

The Spearman rank order coefficient was used to measure associations between continuous variables, since Spearman is less sensitive to outliers than Pearson’s correlation coefficient. Scatter plots were used to check for outliers.

If data were missing in half or less than half of the items within a subscale in the SF-36 questionnaires, the missing values was replaced with the mean score across the completed items in the same subscale. This is in accordance to the SF-36 scoring algorithm referred to by Loge and Kaasa[89].

The six Marsh-Oberhuber grades were collapsed into two categories, Marsh group 1 and Marsh group 2. Marsh grades 0 and 1 in group 1 and Marsh grades 2, 3 a, b and c in group 2. Subjects in group 1 were considered sufficiently treated while subjects in group 2 were considered insufficiently treated. This classification was based on how the gastroenterologists in this project define the histological treatment goal in CD patients (Lundin, oral communication).

4.11 Ethics

The Regional Committee for Medical Research Ethics (REK) and the Privacy Officer for Research at OUS, Rikshospitalet approved the study protocol, see Appendix 10. The participants received written information about the project and signed an informed consent before taking part in the study.
5 Results

5.1 Characteristics of Study Sample

A total of 58 individuals with biopsy proven CD took part in the current study (Figure 4). Twelve participants withdrew from the study, and two participants were excluded because they were close relatives to other participants.

Figure 4. Flow diagram for inclusion of participants to the Celiac Study in Eastern Norway (CELIEN)

Characteristics of the subjects are shown in Table 3. Mean BMI (23.6) was within the normal range. The mean values for waist-hip ratio for women (0.79) and men (0.85) were below the cut-off values. Mean time on a GFD was 21.5 years and was similar as the mean years since CD diagnosis. The participants were predominantly women (44 women, 14 men). Except from two participants, they were all members of NCF, and the majority had a high education (college or more). Individuals that were married or co-habitants (71%) dominated the marital status. Transgression or interruption from the GFD was reported by 36%.
Table 3. Selected characteristics of the study sample. Mean (SD)\(^a\) and (min, max) or number (%), n=58.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Min, max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.9 (14.6)</td>
<td>20, 71</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.7 (11.1)</td>
<td>53, 107</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.3 (0.1)</td>
<td>151, 197</td>
</tr>
<tr>
<td>BMI(^b) (kg/m(^2))</td>
<td>23.6 (3.1)</td>
<td>18, 31</td>
</tr>
<tr>
<td>Waist-hip ratio(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.79 (0.1)</td>
<td>0.69, 0.93</td>
</tr>
<tr>
<td>Men</td>
<td>0.85 (0.1)</td>
<td>0.73, 1.01</td>
</tr>
<tr>
<td>Time since GFD(^d) diagnosis (years)</td>
<td>21.5 (11.8)</td>
<td>10, 59</td>
</tr>
<tr>
<td>Time on GFD(^d) (years)</td>
<td>21.2 (11.4)</td>
<td>9, 59</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>22.0 (17.2)</td>
<td>0, 57</td>
</tr>
<tr>
<td>BMI(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Normal range</td>
<td>37 (63.8)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>17 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>19 (33)</td>
<td></td>
</tr>
<tr>
<td>College/University</td>
<td>19 (33)</td>
<td></td>
</tr>
<tr>
<td>College/university &gt;5 years</td>
<td>17 (29)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/co-habitants</td>
<td>41 (71)</td>
<td></td>
</tr>
<tr>
<td>Singel</td>
<td>17 (29)</td>
<td></td>
</tr>
<tr>
<td>NCF(^e) membership</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56 (97)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Other food allergies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (69)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (14)</td>
<td></td>
</tr>
<tr>
<td>Diet naturally free from gluten</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48 (83)</td>
<td></td>
</tr>
<tr>
<td>Transgression/interruption of GFD(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (36)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37 (64)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) SD, standard deviation
\(^b\) BMI, body mass index. Principal cut-off points: underweight <18.5, normal range 18.5-24.9, overweight >25, obese >30 [99].
\(^c\) Cut-off points: Substantially increased risk of metabolic complications >0.90 (women), >0.85 (men) [97].
\(^d\) GFD, Gluten-free diet
\(^e\) NCF, Norwegian Celiac Society
5.2 Clinical Symptoms

As shown in Table 4, the most prevalent reported symptoms from the Martine questionnaire were: bloating (48.3%), fatigue (51.7%) and breaking wind (56.9%). Figure 5 shows symptoms sorted by prevalence.

Table 4. Reported symptoms during the last four weeks. Martine questionnaire, number (%), n=58.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>28</td>
<td>(48.3)</td>
</tr>
<tr>
<td>Weight change (^b)</td>
<td>4</td>
<td>(6.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9</td>
<td>(15.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22</td>
<td>(37.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>(24.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>(3.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>(44.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>(51.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>23</td>
<td>(39.7)</td>
</tr>
<tr>
<td>Breaking wind</td>
<td>33</td>
<td>(56.9)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>7</td>
<td>(12.1)</td>
</tr>
</tbody>
</table>

\(^a\) Symptoms recorded from item13 in Martine
\(^b\) 1 missing, n =57
Figure 5. Reported symptoms. (%) during the last four weeks. (Martine, item13). Sorted by prevalence, n=58

As presented in Table 5, 9% reported experiencing symptoms daily, similar to the percentage reported never getting symptoms. The percentages reporting getting symptoms weekly, monthly and a few times a year were 26%, 29% and 28%, respectively. Thirty-eight percent reported always getting symptoms if they ingested gluten. As regards gluten sensitivity, 19% reported always, 22% reported rarely and 29% reported never getting symptoms when exposed to even small amounts of gluten (e.g. bread crumbs).
Table 5. Answers on items related to symptom frequency and gluten sensitivity. Martine questionnaire. Number (%), n=58.

<table>
<thead>
<tr>
<th>Items</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 15: How often do you get symptoms?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>5</td>
<td>(9)</td>
</tr>
<tr>
<td>Weekly</td>
<td>15</td>
<td>(26)</td>
</tr>
<tr>
<td>Monthly</td>
<td>17</td>
<td>(29)</td>
</tr>
<tr>
<td>A few times a year</td>
<td>16</td>
<td>(28)</td>
</tr>
<tr>
<td>Never</td>
<td>5</td>
<td>(9)</td>
</tr>
<tr>
<td>Item 16: If you have ingested gluten, do you get symptoms?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>22</td>
<td>(38)</td>
</tr>
<tr>
<td>Often</td>
<td>12</td>
<td>(21)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>13</td>
<td>(22)</td>
</tr>
<tr>
<td>Rarely</td>
<td>7</td>
<td>(12)</td>
</tr>
<tr>
<td>Never</td>
<td>4</td>
<td>(7)</td>
</tr>
<tr>
<td>Item 17: How often do you experience symptoms if you ingest only tiny amounts of gluten, e.g. bread crumbs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>11</td>
<td>(19)</td>
</tr>
<tr>
<td>Often</td>
<td>12</td>
<td>(21)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>5</td>
<td>(9)</td>
</tr>
<tr>
<td>Rarely</td>
<td>13</td>
<td>(22)</td>
</tr>
<tr>
<td>Never</td>
<td>17</td>
<td>(29)</td>
</tr>
</tbody>
</table>

The scores from the symptom specific questionnaires are presented in Table 6. MSS, CSI-, GSRS-IBS- and SHC-scores were consistently low, which mean a tendency of modest symptom complaints. Bloating and diarrhoea were the symptoms from GSRS-IBS with the highest median scores of 5.5 and 5.0, respectively. The scores from SF-36 were in the upper range of the scale, indicative of better health. The scale from SF-36, Change in Health, was an exception where high scores meant that the health had deteriorated over the past year. The scales from SF-36 with the lowest median scores were General Health (77.5) and Bodily Pain (77.8). Vitality had the lowest score of the scales from SF-36, with a mean value of 61.5.
Table 6. Symptom scores. Median (Q₁, Q₃) and mean (SD)³.

<table>
<thead>
<tr>
<th>Symptom specific questionnaire</th>
<th>n</th>
<th>Scoring scale</th>
<th>Median (Q₁, Q₃)</th>
<th>Mean (SD)</th>
<th>Min, max</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS</td>
<td>57</td>
<td>0-11</td>
<td>2.0 (1, 6)</td>
<td>3.4 (2.7)</td>
<td>0-9</td>
</tr>
<tr>
<td>CSI</td>
<td>57</td>
<td>16-80</td>
<td>25.0 (21, 34)</td>
<td>27.9 (8.5)</td>
<td>16-51</td>
</tr>
<tr>
<td>GSRS-IBS</td>
<td>56</td>
<td>13-91</td>
<td>21.0 (16, 29)</td>
<td>24.3 (10.4)</td>
<td>13-59</td>
</tr>
<tr>
<td>Bloating</td>
<td></td>
<td>3-21</td>
<td>5.5 (4, 9.8)</td>
<td>6.4 (3.3)</td>
<td>3-15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>3-21</td>
<td>5.0 (3, 7)</td>
<td>5.7 (3.3)</td>
<td>3-21</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>3-21</td>
<td>4.0 (3, 6)</td>
<td>5.3 (3.3)</td>
<td>3-20</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>2-14</td>
<td>3.0 (2, 5)</td>
<td>3.8 (2.2)</td>
<td>2-10</td>
</tr>
<tr>
<td>Satiety</td>
<td></td>
<td>2-14</td>
<td>2.0 (2, 3)</td>
<td>3.1 (1.9)</td>
<td>2-10</td>
</tr>
<tr>
<td>SHC</td>
<td>58</td>
<td>0-87</td>
<td>7.5 (4,17)</td>
<td>10.7 (8.7)</td>
<td>0-31</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>0-100</td>
<td>77.5 (64, 90)</td>
<td>73.0 (19.8)</td>
<td>73-100</td>
<td></td>
</tr>
<tr>
<td>Change in Health</td>
<td>1-5</td>
<td>3.0 (3, 3)</td>
<td>3.1 (0.6)</td>
<td>2-5</td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>0-100</td>
<td>97.5 (90, 100)</td>
<td>93.8 (8.0)</td>
<td>70-100</td>
<td></td>
</tr>
<tr>
<td>Role-Physical</td>
<td>0-100</td>
<td>100.0 (75, 100)</td>
<td>80.6 (32.1)</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>0-100</td>
<td>100.0 (67, 100)</td>
<td>85.3 (29.0)</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>0-100</td>
<td>100.0 (86, 100)</td>
<td>90.2 (18.4)</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>0-100</td>
<td>77.8 (56, 100)</td>
<td>73.6 (25.0)</td>
<td>11-100</td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>0-100</td>
<td>82.0 (75, 92)</td>
<td>80.3 (13.1)</td>
<td>40-100</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>0-100</td>
<td>65.0 (45, 80)</td>
<td>61.5 (22.2)</td>
<td>0-100</td>
<td></td>
</tr>
</tbody>
</table>

MSS=Martine Symptom Score, CSI=Celiac Symptom Index, GSRS-IBS=Gastro intestinal Symptom Rating Scale-Irritable Bowel Syndrome, SHC= Subject Health Complaints, SF-36=Short Form-36

³ Q₁ 25th percentile, Q₃ 75th percentile

When considering the SHC form as a whole, 96.6% reported having at least one subjective health complaint (score > 0) during the last three days. When comparing the subscales, gastrointestinal complaints were shown most troubling with 82.8% reported having at least one gastrointestinal symptom (Table 7). Furthermore, musculoskeletal and pseudoneurological complaints were reported by 81.0% and 74.1%, respectively. Allergy (36.2%) and flu (29.3%) were less prevalent.

Table 7. Percentage of subjects reporting minimum one health complaint (score>0) in the four subscales of SHC#. Number (%), n=58.

<table>
<thead>
<tr>
<th>Subscale complaints</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>48</td>
<td>(82.8)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>47</td>
<td>(81.0)</td>
</tr>
<tr>
<td>Pseudoneurological</td>
<td>43</td>
<td>(74.1)</td>
</tr>
<tr>
<td>Allergic</td>
<td>21</td>
<td>(36.2)</td>
</tr>
<tr>
<td>Flu</td>
<td>17</td>
<td>(29.3)</td>
</tr>
</tbody>
</table>

# SHC, Short Health Form
5.2.1 Clinical Symptoms and Intestinal Histology

As shown in Table 8, 72% of the study sample had Marsh grade 0. The majority (82.3%) had histological findings consistent with a successfully treated CD, comprising Marsh grades 0 and 1 (Marsh group 1). Subjects with considerable intestinal lesions comprised a much smaller proportion (17.2%) (Marsh group 2). No one was classified as having Marsh grade 3c.

Table 8. Marsh-Oberhuber classification divided into two groupsa. Number (%).

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>(%)</th>
<th>Group</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh grade 0</td>
<td>42</td>
<td>(72.4)</td>
<td>1</td>
<td>48</td>
<td>(82.8)</td>
</tr>
<tr>
<td>Marsh grade 1</td>
<td>6</td>
<td>(10.3)</td>
<td>1</td>
<td>48</td>
<td>(82.8)</td>
</tr>
<tr>
<td>Marsh grade 2</td>
<td>2</td>
<td>(3.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsh grade 3a</td>
<td>4</td>
<td>(6.9)</td>
<td>2</td>
<td>10</td>
<td>(17.2)</td>
</tr>
<tr>
<td>Marsh grade 3b</td>
<td>4</td>
<td>(6.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Division based on definition of histological treatment goal in CD patients

No statistical significant differences were observed in test scores from MSS, CSI, SHC, GSRS-IBS and SF-36 between the two Marsh groups, except from Role-Physical, where the group showing intestinal lesions had a significant lower score (p=0.004), meaning poorer ability of working and accomplishing tasks (Table 9). The results from CSI, GSRS-IBS, Role-Emotional and Bodily Pain indicated some differences between the two groups, but the differences were not significant.
### Table 9. Symptom scores by Marsh groups. Data are given as median (Q₁, Q₃)\(^a\)

<table>
<thead>
<tr>
<th>Symptom Score</th>
<th>Marsh, group 1(^b)</th>
<th>Marsh, group 2(^c)</th>
<th>p-value(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS</td>
<td>2.5 (1, 6)</td>
<td>2 (0.5, 5)</td>
<td>0.80</td>
</tr>
<tr>
<td>CSI</td>
<td>25.0 (20, 32)</td>
<td>30.0 (25, 38)</td>
<td>0.06</td>
</tr>
<tr>
<td>GSRS-IBS</td>
<td>21.0 (16, 29)</td>
<td>29.0 (20, 37)</td>
<td>0.07</td>
</tr>
<tr>
<td>SHC</td>
<td>7.0 (3, 17)</td>
<td>10.0 (8, 21)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**SF-36**

|  | General Health | 77.5 (58, 90) | 77.5 (64, 88) | 0.84 |
|  | Change in Health | 3 (3, 3) | 3 (3, 3) | 0.28 |
|  | Physical Functioning | 100 (90, 100) | 95 (89, 100) | 0.45 |
|  | Role-Physical | 100 (75, 100) | 50 (0, 100) | **0.004** |
|  | Role-Emotional | 100 (100, 100) | 83.3 (58, 100) | 0.07 |
|  | Social Functioning | 100 (88.9, 100) | 88.9 (72.2, 100) | 0.26 |
|  | Bodily Pain | 83.3 (55.6, 100) | 55.5 (33.3, 88.9) | 0.08 |
|  | Mental Health | 82 (76, 92) | 82 (66, 93) | 0.84 |
|  | Vitality | 67.5 (45, 80) | 52.5 (33.8, 76.3) | 0.23 |

MSS=Martine Symptom Score, CSI=Celiac Symptom Index, GSRS-IBS=Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome, SHC= Subject Health Complaints, SF-36=Short Form-36

\(^a\)Q₁ 25\(^{th}\) percentile, Q₃ 75\(^{th}\) percentile

\(^b\)Marsh group 1: Marsh grades 0 and 1

\(^c\)Marsh group 2: Marsh grades 2, 3 a, b and c

\(^d\)Mann-Whitney U Test

\(^e\)Marsh group 1: CSI 1 missing, n=47, GSRS-IBS 2 missing, n=46

\(^f\)Marsh group 2: MSS 1 missing, n=9
5.2.2 Clinical Symptoms and GFD adherence

GFD adherence, measured as CDAT score, had a median score of 11 (Q₁, 10, Q₃, 15). Higher scores represent worse GFD adherence (score <13 = adequate GFD adherence, score ≥13 = inadequate GFD adherence). MSS, CSI and SHC correlated significantly with CDAT score (Table 10), implying that subjects with high score on CDAT, meaning inadequate GFD adherence, reported more symptoms and health complaints than subjects with low CDAT score.

From SF-36, there were significant correlations between CDAT score for six out of nine of the scales: General Health, Role-Physical, Role-Emotional, Social Functioning, Bodily Pain and Vitality, implying that subjects with low score on CDAT, meaning adequate GFD adherence, reported fewer symptoms and health complaints than subjects with high CDAT score.

Table 10. Spearman correlation between GFD adherence a and clinical symptoms.

<table>
<thead>
<tr>
<th>Symptom questionnaire</th>
<th>n</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS</td>
<td>57</td>
<td>0.31</td>
<td>0.02</td>
</tr>
<tr>
<td>CSI</td>
<td>57</td>
<td>0.37</td>
<td>0.005</td>
</tr>
<tr>
<td>GSRS-IBS</td>
<td>56</td>
<td>0.16</td>
<td>0.23</td>
</tr>
<tr>
<td>SHC</td>
<td>58</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>SF-36</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>-0.32</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Change in Health</td>
<td>0.04</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>-0.23</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Role-Physical</td>
<td>-0.33</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>-0.35</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>-0.32</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>-0.32</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>-0.19</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>-0.39</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

MSS=Martine Symptom Score, CSI=Celiac Symptom Index, GSRS-IBS=Gastro intestinal Symptom Rating Scale-Irritable Bowel Syndrome, SHC= Subject Health Complaints, SF-36=Short Form-36

a GFD adherence measured by CDAT-score
b Spearman’s rank correlation
The CDAT score was also categorized as adherent (< 13) and non-adherent (≥13) and tested against the symptom scores. There were significant differences in scores from MSS, CSI, SHC, Role-Physical, Role-Emotional, Bodily Pain and Vitality between the adherent and the non-adherent group (Table 11). The adherent group reported less symptoms compared to the non-adherent group. This is illustrated for MSS, SHC, CSI and Vitality in Figure 6.

Table 11. Symptom score in two groups, adherent and non-adherent. Median (Q₁, Q₃)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Adherent(^b)</th>
<th>Non-adherent(^c),</th>
<th>p-value(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 34(^e)</td>
<td>n=24(^e)</td>
<td></td>
</tr>
<tr>
<td>Median (Q₁, Q₃)(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSS</td>
<td>2 (1.4)</td>
<td>5 (1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>CSI</td>
<td>24.5 (19.8, 32)</td>
<td>31 (23, 41)</td>
<td>0.03</td>
</tr>
<tr>
<td>GSRS-IBS</td>
<td>19.5 (16, 28.5)</td>
<td>23.5 (18, 29.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>SHC</td>
<td>6 (3, 12.5)</td>
<td>8.5 (6.3, 22)</td>
<td>0.03</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>80 (68.8, 90)</td>
<td>70 (46.3, 85)</td>
<td>0.13</td>
</tr>
<tr>
<td>Change in Health</td>
<td>3 (3, 3)</td>
<td>3 (3, 3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>100 (90, 100)</td>
<td>95 (86.3, 100)</td>
<td>0.22</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>100 (100, 100)</td>
<td>75 (50, 100)</td>
<td>0.02</td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>100 (100, 100)</td>
<td>100 (41.7, 100)</td>
<td>0.045</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>100 (88.9, 100)</td>
<td>100 (77.8, 100)</td>
<td>0.08</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>88.9 (63.9, 100)</td>
<td>66.7 (44.4, 88.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mental Health</td>
<td>84 (76, 89)</td>
<td>76 (65, 92)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vitality</td>
<td>72.5 (50, 80)</td>
<td>50 (35, 70)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

MSS=Martine Symptom Score, CSI=Celiac Symptom Index, GSRS-IBS=Gastro intestinal Symptom Rating Scale-Irritable Bowel Syndrome, SHC= Subject Health Complaints, SF-36=Short Form-36
\(^a\) Q₁ 25\(^{th}\) percentile, Q₃ 75\(^{th}\) percentile
\(^b\) Adherent (CDAT-score<13),
\(^c\) Non-adherent (CDAT-score ≥13)
\(^d\) Adherent group GSRS-IBS;2 missing, n=32
\(^e\) Non-adherent group. MSS;1 missing, n=23, CSI;1 missing, n=23
\(^f\) Mann-Whitney U Test
**Figure 6.** Box plots of symptom scores in the adherent and non-adherent group. a) Martine Symptom Score. b) Celiac Symptom Index. c) Subject Health Complaints. d) Vitality (SF-36)
5.3 Nutrient Intake

5.3.1 Nutrient Intake in relation to the Nordic Nutritional Recommendations (NNR)

Determination of underreporting

Goldberg ´s cut-off [96] was applied to our sample; comprising about 50 subjects completing a four day weighed food record, to estimate PAL cut-off. This gave a PAL cut-off of 1.48. The ratio between mean intake and mean BMR in our study sample gave a PAL of 1.45. The deviation between these two PAL values suggested that some under-reporting had occurred.

Macronutrients

The women´s mean and median energy proportion from total fat was 41.5% and 42.0%, respectively, and above the recommended levels (Table 12a). The intake of saturated fatty acids was also high, mean 14.6% and median 14%. The mean and median values of energy proportions from carbohydrates showed 40-41%, which is 10E% below lower than recommended. The energy percentage from protein was adequate, mean 16.8E% and median 16.0E%. Additionally, the intake of mono– and polyunsaturated fatty acids, trans-fatty acids and sugar were within the recommendations. When comparing intake of dietary fibre with the recommendations, the mean and median intake was roughly 4 grams below the lower limit of recommended levels.

The men showed a mean and median intake of saturated fatty acids of 12E% and 13E%, respectively. This was above the upper range of the recommended level, while the intake of mono- and poly unsaturated fatty acids was slightly below the lower range of recommended levels, mean 9.8 E% and median 9E% and mean 5E% and median 4E%, respectively (Table 12b). The intake of total fat, proteins and carbohydrates were in accordance to the recommendations.

Micronutrients

In women, the median value of iron showed an insufficient intake of roughly 10 mg per day (Table 12a). The median value of daily vitamin D intake was 4.7μg, about 3 μg below
recommended level. The mean and median daily intake of the fat-soluble vitamins, vitamin A and vitamin E were above the recommended levels. Daily folate intake did not meet the recommendation. The mean and median values were 274 µg and 235µg, respectively. The phosphorus intake was above the recommended level, the mean and median levels were in the range 1200-1300 mg.

In men, the median intake of vitamin A and vitamin E were below the recommended levels, 8.2 RE and 757 α-TE, respectively (Table 12b). The mean and median daily intakes of folate were below the recommended levels, 266 µg and 228 µg, respectively. The daily intake of phosphorus was above the recommended level, mean and median values were 1337 mg and 1265 mg, respectively.
Table 12a. Daily nutrient intake compared to the recommendations. Mean (SD) and median (Q₁, Q₃). n=42

<table>
<thead>
<tr>
<th>Macronutrients, (E%)</th>
<th>CELIEN®, 2012</th>
<th>NNR²</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (Q₁, Q₃)</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>41.5 (9.5)</td>
<td>42 (36, 47)</td>
<td>25-35</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>14.6 (4.5)</td>
<td>14 (11, 18)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>13.6 (4.9)</td>
<td>14 (9, 17)</td>
<td>10-15</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>6.8 (3.6)</td>
<td>6 (4, 9)</td>
<td>5-10</td>
</tr>
<tr>
<td>Trans-fatty acids</td>
<td>0.38 (0.49)</td>
<td>0.00 (0.0, 1.0)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Protein</td>
<td>16.8 (3.6)</td>
<td>16 (14, 19)</td>
<td>10-20</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>40 (10)</td>
<td>41 (35, 47)</td>
<td>50-60</td>
</tr>
<tr>
<td>Sugar</td>
<td>5 (4)</td>
<td>5 (1, 7)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Dietary fibre (g)</td>
<td>22 (10)</td>
<td>21 (15, 25)</td>
<td>25-35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (RE)⁵</td>
<td>990 (720)</td>
<td>837 (435, 1285)</td>
<td>700</td>
</tr>
<tr>
<td>Vitamin D (µg)</td>
<td>7.9 (9.3)</td>
<td>4.7 (2.7, 10.7)</td>
<td>7.5</td>
</tr>
<tr>
<td>Vitamin E (α-TE)⁶</td>
<td>24 (61.4)</td>
<td>11.6 (6.6, 18)</td>
<td>8</td>
</tr>
<tr>
<td>Thiamine (mg)</td>
<td>1.4 (1.1)</td>
<td>1.1 (0.9, 1.5)</td>
<td>1.1</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>1.8 (1.2)</td>
<td>1.5 (1.1, 2.0)</td>
<td>1.3</td>
</tr>
<tr>
<td>Niacin (NE)⁸</td>
<td>32 (11.9)</td>
<td>29 (24, 38)</td>
<td>15</td>
</tr>
<tr>
<td>B₆ (mg)</td>
<td>2.2 (2.3)</td>
<td>1.6 (1.1, 2.2)</td>
<td>1.2</td>
</tr>
<tr>
<td>Folate (µg)</td>
<td>274 (154)</td>
<td>235 (151, 339)</td>
<td>300³</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>177 (204)</td>
<td>123 (78, 200)</td>
<td>75</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>787 (253)</td>
<td>797 (590, 924)</td>
<td>800</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>1337 (439)</td>
<td>1265 (1102, 1608)</td>
<td>600</td>
</tr>
<tr>
<td>Potassium (g)</td>
<td>3.0 (1.1)</td>
<td>2.9 (2.5, 3.6)</td>
<td>3.1</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>19.5 (43)</td>
<td>9.8 (7.4, 13.0)</td>
<td>15</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>10.3 (4.7)</td>
<td>8.5 (7.2, 11.6)</td>
<td>7</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>59 (36)</td>
<td>47 (36, 71)</td>
<td>40</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>311 (164)</td>
<td>269 (212, 379)</td>
<td>280</td>
</tr>
</tbody>
</table>

¹The Celiac Study in Eastern Norway
²The values are based on a reference group of females, 31-60 years.
³SD, standard deviation
⁴Q 25th percentile, Q 75th percentile
⁵RE, Retinol equivalents; 1 retinol equivalent (RE)=1µg retinol=12 µg β-carotene
⁶α-TE, α-tocopherol equivalents; 1 α-tocopherol equivalent =1mg RRR- α-tocopherol
⁷NE, Niacin equivalent= 1 mg niacin=60 mg tryptophan
⁸Women of reproductive age are recommended a daily intake of 400µ
Table 12b. Daily nutrient intake compared to the recommendations. Mean (SD) and median (Q₁, Q₃). n=13.

<table>
<thead>
<tr>
<th></th>
<th>CELIEN&lt;sup&gt;a&lt;/sup&gt;, 2012</th>
<th>NNR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Median (Q₁, Q₃)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Macronutrients, (E%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>32 (7.2)</td>
<td>30 (26, 38)</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>12 (3.0)</td>
<td>13 (9, 15)</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>9.8 (2.8)</td>
<td>9 (7, 12)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>5 (2.3)</td>
<td>4 (3, 8)</td>
</tr>
<tr>
<td>Trans-fatty acids</td>
<td>0.4 (0.5)</td>
<td>0.00 (0.0, 1.0)</td>
</tr>
<tr>
<td>Protein</td>
<td>15.8 (3.06)</td>
<td>15 (14, 19)</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>50.6 (8.9)</td>
<td>51 (43, 58)</td>
</tr>
<tr>
<td>Sugar</td>
<td>7.8 (3.4)</td>
<td>7 (5, 11)</td>
</tr>
<tr>
<td>Dietary fibre (g)</td>
<td>25.1 (10.4)</td>
<td>25.5 (16, 32)</td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A (RE)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>898 (588)</td>
<td>757 (446, 1217)</td>
</tr>
<tr>
<td>Vitamin D (µg)</td>
<td>7.3 (6.0)</td>
<td>7.2 (2.8, 9.1)</td>
</tr>
<tr>
<td>Vitamin E (α-TE)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>11.9 (8.5)</td>
<td>8.2 (5.2, 14.5)</td>
</tr>
<tr>
<td>Thiamine (mg)</td>
<td>1.34 (0.3)</td>
<td>1.35 (1.0, 1.6)</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>1.9 (0.7)</td>
<td>1.8 (1.4, 2.3)</td>
</tr>
<tr>
<td>Niacin (NE)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>34.4 (11.6)</td>
<td>31.5 (25, 41.5)</td>
</tr>
<tr>
<td>B₆ (mg)</td>
<td>1.9 (0.6)</td>
<td>1.8 (1.5, 2.0)</td>
</tr>
<tr>
<td>Folate (µg)</td>
<td>266 (98)</td>
<td>228 (188, 362)</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>175 (169)</td>
<td>112 (58, 203)</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>1080 (574)</td>
<td>995 (775, 1182)</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>1581 (495)</td>
<td>1450 (1344, 1608)</td>
</tr>
<tr>
<td>Potassium (g)</td>
<td>3.7 (0.9)</td>
<td>3.6 (3.3, 4.3)</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>10.4 (4.5)</td>
<td>9.2 (7.4, 13)</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>9.9 (3.4)</td>
<td>9.1 (7.2, 12.2)</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>48 (13.5)</td>
<td>47 (40, 60)</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>339 (87)</td>
<td>330 (293, 386)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The Celiac Study in Eastern Norway  
<sup>b</sup> The values are based on a reference group of males, 31-60 years.  
<sup>c</sup> SD, standard deviation  
<sup>d</sup> Q₅₀, 25<sup>th</sup> percentile, Q₇₅, 75<sup>th</sup> percentile  
<sup>e</sup> RE, Retinol equivalents; 1 retinol equivalent (RE)=1 µg retinol=12 µg β-carotene  
<sup>f</sup> α-TE, α-tocopherol equivalents; 1 α-tocopherol equivalent =1mg RRR- α-tocopherol  
<sup>g</sup> NE, Niacin equivalent= 1 mg niacin=60 mg tryptophan
Figure 7 shows the percentage of women and men who did not reach the recommended daily intake of nutrients identified as insufficient. The intake of these nutrients was below the recommended levels, with the exception of total fat and saturated fat with intakes above the recommendations.

Figure 7. Nutrient intake below the recommended levels in percentage of women and men.

Mean and median values of daily intake of nutrients of the total study sample can be found in Appendix 11.

5.3.2 Clinical Symptoms and Nutrient Intake

There were significant negative correlations between CSI scores and the percentage of energy from proteins in the diet ($r=-0.34$, $p=0.01$) and intake of calcium ($r=-0.28$, $p=0.04$), with more symptoms associated with a lower percentage of energy from proteins and lower intake of calcium (Table 13). There was a significant positive correlation between General Health score from SF-36 and the percentage of energy from proteins in the diet ($r=0.41$, $p<0.01$) and intake of calcium ($r=0.29$, $p=0.03$), with better general health associated with a higher percentage of energy from proteins and higher intake of calcium. The score from Physical
Functioning was significant inversely correlated with percentage of energy from saturated fatty acids ($r=-0.30, p=0.03$) and significant positively correlated with intake of proteins ($r=0.27, p=0.05$), with better physical functioning associated with a higher energy percentage from proteins and lower energy percentage from saturated fatty acids. There was a significant negative correlation between Role-Emotional score and intake of carbohydrates ($r=-0.28, p=0.04$), with higher scores on Role-Emotional associated with a lower percentage of energy from carbohydrates.
Table 13. Spearman correlation between energy- and nutrient intake and symptom scores. n=54

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>CSI</th>
<th>GSRS-IBS</th>
<th>SHC</th>
<th>SF-36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GH</td>
<td>CH</td>
<td>PF</td>
<td>RP</td>
<td>RE</td>
</tr>
<tr>
<td>Energy (kJ)</td>
<td>0.15</td>
<td>0.05</td>
<td>0.04</td>
<td>0.01</td>
<td>-0.07</td>
</tr>
<tr>
<td>Fat (E%)</td>
<td>0.03</td>
<td>0.14</td>
<td>0.12</td>
<td>0.10</td>
<td>-0.07</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>-0.11</td>
<td>0.16</td>
<td>-0.02</td>
<td>0.10</td>
<td>-0.07</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>-0.01</td>
<td>0.17</td>
<td>0.13</td>
<td>0.16</td>
<td>-0.12</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>-0.18</td>
<td>-0.14</td>
<td>-0.09</td>
<td>-0.05</td>
<td>-0.05</td>
</tr>
<tr>
<td>Proteins (E%)</td>
<td>-0.17</td>
<td>-0.34a</td>
<td>-0.27</td>
<td>-0.13</td>
<td>0.41a</td>
</tr>
<tr>
<td>Carbohydrates (E%)</td>
<td>0.04</td>
<td>0.01</td>
<td>0.00</td>
<td>-0.07</td>
<td>-0.04</td>
</tr>
<tr>
<td>Sugar</td>
<td>-0.02</td>
<td>-0.09</td>
<td>-0.12</td>
<td>-0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Dietary fibre (g)</td>
<td>0.06</td>
<td>0.02</td>
<td>0.16</td>
<td>-0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Vitamin d (µg)</td>
<td>-0.06</td>
<td>-0.09</td>
<td>-0.06</td>
<td>-0.11</td>
<td>-0.01</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>-0.23</td>
<td>-0.28a</td>
<td>-0.21</td>
<td>-0.21</td>
<td>0.29a</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>-0.03</td>
<td>0.06</td>
<td>0.07</td>
<td>0.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Selenium (mg)</td>
<td>-0.08</td>
<td>-0.15</td>
<td>-0.12</td>
<td>-0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Zinc (µg)</td>
<td>-0.03</td>
<td>-0.15</td>
<td>0.01</td>
<td>0.08</td>
<td>0.05</td>
</tr>
</tbody>
</table>

MSS=Martine Symptom Score, CSI=Celiac Symptom Index, GSRS-IBS=Gastro intestinal Symptom Rating Scale-Irritable Bowel Syndrome, SHC= Subject Health Complaints, SF-36=Short Form-36; GH=General Health, CH=Change in Health, PH=Physical Functioning, RP=Role Physical, RE=Role Emotional, SF=Social Functioning, BP=Bodily Pain, MH=Mental Health, VT=Vitality

*p<0.05
Energy percentage from proteins showed a relation with three of the symptom scales. The strongest relationship between nutrient intake and symptom scores were seen between CSI score and *General Health* score with energy percentage from proteins. Scatter plots of CSI score and *General Health* score by energy percentage from proteins are presented in Figure 8a-b.

![a)

Figure 8. Scatter plots of a) CSI score and b) *General Health* score with protein intake (R= -0.34, p=0.01 and R=0.41, p=0.002, respectively)
5.3.3 Intestinal Histology and Nutritional Status

The variables reflecting nutritional status; BMI, body weight, waist-hip ratio are shown in Table 3. Serum levels of micronutrients were within adequate levels according to the reference levels used by the respective laboratories (see also 4.8.2), in both women and men. Serum levels of micronutrients are presented in Appendix 12.

As shown in Table 14 and 15, there were no significant differences in body weight, height, BMI, waist-hip ratio or serum levels of micronutrients between Marsh groups. Serum level of total cholesterol and LDL-C indicated some differences between the two Marsh groups, but the differences were not significant.

**Table 14. Anthropometrics by Marsh groups, Median (Q₁, Q₃)**

<table>
<thead>
<tr>
<th></th>
<th>Marsh, group 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Marsh, group 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median, (Q₁, Q₃)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Median, (Q₁, Q₃)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>67  (58, 76)</td>
<td>70  (65, 82)</td>
<td>0.18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 (163, 175)</td>
<td>172 (167, 179)</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;e&lt;/sup&gt; (kg/m²)</td>
<td>23  (21, 26)</td>
<td>24  (22, 27)</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist-hip ratio&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.78 (0.76, 0.83)</td>
<td>0.80 (0.77, 0.91)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

<sup>a</sup> Marsh group 1: Marsh grades 0 and 1  
<sup>b</sup> Marsh group 2: Marsh grades 2, 3 a, b and c  
<sup>c</sup> Mann-Whitney U Test  
<sup>d</sup> Q₁ 25<sup>th</sup> percentile, Q₃ 75<sup>th</sup> percentile  
<sup>e</sup> Body mass index. Principal cut-off points: underweight <18.5, normal range 18.5-24.9, overweight >25, obese >30  
<sup>f</sup> Cut-off points: Substantially increased risk of metabolic complications >0.90 (women), >0.85 (men)
Table 15. Serum micronutrients by Marsh groups. Median (Q₁, Q₃)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Marsh, group 1ᵃ</th>
<th>Marsh, group 2ᵇ</th>
<th>p-valueᵈ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>46</td>
<td>18 (16, 23)</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>48</td>
<td>13.9 (13.6, 14.9)</td>
<td>10</td>
</tr>
<tr>
<td>Ferritin</td>
<td>46</td>
<td>71 (46, 146)</td>
<td>10</td>
</tr>
<tr>
<td>Transferrin</td>
<td>46</td>
<td>2.6 (2.4, 2.9)</td>
<td>10</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>46</td>
<td>0.28 (0.25, 0.34)</td>
<td>10</td>
</tr>
<tr>
<td>Folate</td>
<td>48</td>
<td>20.0 (16.0, 30.8)</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>46</td>
<td>353 (261, 511)</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>43</td>
<td>57 (43, 85)</td>
<td>6</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>48</td>
<td>10 (8, 11)</td>
<td>10</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>47</td>
<td>5.0 (4.6, 5.5)</td>
<td>10</td>
</tr>
<tr>
<td>LDL-Cᵉ</td>
<td>47</td>
<td>2.9 (2.4, 3.6)</td>
<td>10</td>
</tr>
<tr>
<td>HDL-Cᶠ</td>
<td>47</td>
<td>1.7 (1.4, 2.0)</td>
<td>10</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>47</td>
<td>0.7 (0.6, 0.9)</td>
<td>9</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>47</td>
<td>1.80 (1.5, 2.0)</td>
<td>10</td>
</tr>
<tr>
<td>Calcium</td>
<td>48</td>
<td>2.27 (2.21, 2.29)</td>
<td>10</td>
</tr>
<tr>
<td>Adj.caliumᵍ</td>
<td>42</td>
<td>1.22 (1.20, 1.24)</td>
<td>8</td>
</tr>
<tr>
<td>25-OH-Vit.Dʰ</td>
<td>43</td>
<td>70 (55, 83)</td>
<td>9</td>
</tr>
<tr>
<td>1.25-OH-Vit.Dⁱ</td>
<td>43</td>
<td>126 (102, 148)</td>
<td>9</td>
</tr>
<tr>
<td>Magnesium</td>
<td>46</td>
<td>0.82 (0.79, 0.86)</td>
<td>9</td>
</tr>
<tr>
<td>Selenium</td>
<td>37</td>
<td>1.0 (0.9, 1.2)</td>
<td>7</td>
</tr>
<tr>
<td>Zinc</td>
<td>46</td>
<td>14 (13, 16)</td>
<td>9</td>
</tr>
</tbody>
</table>

ᵃMarsh group 1: Marsh grade 0 and 1
ᵇMarsh group 2: Marsh grade 2, 3 a, b and c
ᵈQ₁, 25th percentile, Q₃, 75th percentile
ᵉMann-Whitney U-Test
ᶠLow density lipoprotein cholesterol
ᵍHigh density lipoprotein cholesterol
ʰAlbumin adjusted calcium
ʰ²5-dihydroxy vitamin D
ⁱ1.25- dihydroxy vitamin D
6 Discussion

6.1 Summary of Results

Clinical symptoms and health complaints were reported to a small extent in the current study, in terms of severity and impact on health. According to MSS, the most prevalent symptoms were breaking wind, bloating and diarrhoea. The results from GSRS-IBS revealed that gastrointestinal symptoms were of minor discomfort. Gastrointestinal and musculoskeletal complaints were the most bothersome according to the SHC inventory. Both physical and mental health measured by SF-36 was fairly good. Vitality, General Health and Bodily Pain were scales with lowest scores.

There was a significant difference in symptom score Role-Physical (SF-36), between the group with normal intestinal histology and the group with pathological features, with improved ability of working and accomplishing tasks in the group with normal histology. The adherent and non-adherent group differed significantly on several symptom scales, with more symptoms reported in the non-adherent group. According to the NNR, the nutrient intake was insufficiently covered regarding iron and dietary fibre in women, vitamin A and vitamin E in men and folate and vitamin D in both genders. The energy percentage from fat was above the recommended levels in women. A more favourable intake, regarding the energy yielding nutrients was found in men. It was seen a relation between increased percentage of energy from proteins and higher intake of calcium with fewer symptoms and less health complaints.

6.2 Sample and Recruitment

We planned a sample size of 68 subjects to obtain a sufficient statistical power (see 3.1). This was not achieved due to a 17% withdrawal and exclusion of two subjects who did not fulfil the criteria of independency. Additionally, celiac patients from other areas than Eastern Norway were not allowed to participate, which limited the sample size further. This was partly due to economical restrictions and to avoid interference with the areas comprised by the CIA. The final study sample consisted of 58 subjects, which provided us a statistical power of 86% for comparison of two equal sized groups. Due to an unequal sample size in the two Marsh groups, the statistical power was considerably reduced when comparing differences.
between Marsh groups. Hence, the results should be considered with caution. The adherent and non-adherent groups were of more equal sizes, consequently the statistical power remains fairly good. Since the subjects only represented the Eastern part of Norway, we must be careful when drawing conclusions on behalf of the Norwegian celiac population.

The study sample had an uneven gender distribution. Women comprised 76% of the sample. CD is more prevalent in women than in men [100, 101]. A twofold larger prevalence has been estimated. This can partly justify the uneven distribution. The level of education was skewed toward higher education. This implies better health literacy and could therefore be a strength to this study as it involves an increased probability of completing the tasks appropriately. On the other hand, it may suggest a selection bias. Married/cohabitant (71%) subjects dominated the marital status, which may affect both symptom prevalence and GFD adherence.

The subjects were recruited mainly through NCF. Only two subjects were not members. Recruiting study participants through an advocacy group may limit the representativeness. Leffler et al. identified membership of a celiac advocacy group as a factor that facilitates GFD adherence [12]. It is also timely to question the representativeness of the sample when the individuals voluntarily signed up for participation, inevitable when recruiting participants for medical research. Another aspect is that participation in this study involved a promise of a thoroughly medical check, which may appeal to a specific group within the celiac population, namely individuals who are particularly concerned with their own health and therefore may be more strictly adhering to the GFD. Judging by the division from the CDAT cut-off, 34 subjects were classified as adherent while 24 were classified as non-adherent. Another possibility is that celiac patients who are experiencing more symptoms saw a greater benefit of participating in the study and that symptom prevalence therefore may be higher than the true prevalence.
6.3 Results

6.3.1 Clinical Symptoms

**MSS and items related to gluten sensitivity**

The majority of the current study sample comprised CD patients with an overt clinical presentation, representing the classical phenotype. Five subjects reported never experiencing symptoms and four subjects claimed that even after gluten ingestion, they never got symptoms, equal with asymptomatic CD. The identification of some asymptomatic subjects in the sample was not surprising, as it has been proposed that a large fraction of the CD population do not manifest classic symptoms [33, 34]. The symptoms reported most frequently from MSS were bloating, fatigue and breaking wind. These are commonly reported symptoms in CD. The majority of the sample reported to experience symptoms monthly, while 9% answered that they were experiencing symptoms on a daily basis. Almost half of the sample reported being fairly sensitive to even tiny amounts of gluten, suggesting that many may experience symptoms accidentally. Noteworthy in this context, we found that the GFD adherent group had less symptoms and health complaints than the non-adherent group, implying that symptoms likely is a result of inadequate GFD adherence, and not just a consequence of accidental ingestion of small amounts of gluten.

**GSRS-IBS**

GSRS-IBS does not have any cut-off value, but the median (21.0) and mean (24.3) symptom scores, were almost similar to the mean score (25) found at baseline in a recent study on Norwegian celiac patients [86]. This underpins the reliability of our finding. Importantly, the CD patients in this recently conducted study shared many of the characteristics of our study sample in terms of age, place of residence and method of recruitment, which may explain the coincidence. Still, the similar finding is of value as it can be extended to a larger group of CD patients from Eastern Norway.

Bloating and diarrhea were the symptoms reported to be the most severe. Notably, the median scores were only 5.5 and 5.0, respectively, implying only minor complaints. Constipation, pain and satiety seemed to be negligible. Interestingly, based on MSS, bloating and diarrhea were some of the more frequently reported symptoms, but GSRS-IBS to judge, of mild discomfort.
The median sum score from SHC was 7.5 and hence very low, considering that the highest possible sum score was 87, implying that health complaints were only modestly present in our sample. Notably, median and mean (10.7) symptom scores from SHC were almost similar to SHC scores measured at baseline in a recent study on Norwegian celiac patients showing a mean score of 10 [86]. This parallel may strengthen the applicability of our findings.

Ihlebæk et al. studied the prevalence of subjective health complaints among a sample of Norwegians representing the general population and 96.2% reported any health complaints [102]. This is in accordance with our result of 96.6% reporting any subjective health complaints. When comparing results from the different subscales, 83% reported having gastrointestinal problems in the current study compared to 60% of the general population, which was a considerable difference. This suggests that gastrointestinal problems are more prevalent in treated CD patients than in the general population, which is in agreement with findings from a Swedish study [85]. The Swedish researchers studied the occurrence of gastrointestinal symptoms in adults with CD, treated with GFD for several years and found that women, in particular, had more symptoms than controls of same gender [85]. In Ihlebæk’s study sample, women reported more complaints than men regarding musculoskeletal and pseudoneurological complaints [102]. This may imply that our results as regards these complaints in CD patients may be overestimated, considering that women comprised the majority of the sample.

**SF-36**

The current study showed excellent scores on *Physical Functioning*, *Role-Physical*, *Role-Emotional* and *Social Functioning* scales from SF-36. *Vitality* scale score (65) was lowest, implying that the other scale scores were very good. SF-36 has been performed in a sample representing the general Norwegian population and the results were presented separately for women and men [89]. Division by gender was not made in the current study. The mean scores for women and men from the general population were in the following ranges: 76-77 (*General Health*), 85-90 (*Physical Functioning*), 75-81 (*Role-Physical*), 79-85 (*Role-Emotional*), 84-88 (*Social Functioning*), 73-77 (*Bodily Pain*), 78-80 (*Mental Health*) and 57-63 (*Vitality*). Whether our median values are comparable to the mean values from the reference population can be doubted. However, it would not be appropriate to use the mean values solely, as the variables were not normally distributed. When considering both median
and mean values, our results were fairly similar to the general population. Note that the scales: Role-Physical, Role-Emotional and Social-Functioning differed considerably in median and mean scores.

Considering that our sample consisted of individuals with a chronic disease, it was reasonable to expect poorer health in terms of physical function and well-being compared to a reference population of apparently healthy individuals. The reference group was considerably larger than our study sample, which implies a greater diversity. Additionally, our study sample may have been subject to selection bias; comprising subjects with particularly concern with own health, which may account for the lack of difference between the two groups.

In the general population, women had lower scores than men on all scales [89]. Level of education was found to have a significant influence on all scale scores, with higher levels of education associated with higher scores. Marital status was also found to affect scale scores, with married/cohabitant subjects having higher scores. These findings may have implications for our results, since our study sample was overrepresented by women, subjects with higher levels of education and married/cohabitant subjects. The two latter may explain why our sample of “chronic ill” subjects reached the levels of a general population, while the predominance of women could accordingly affect the results in opposite direction, resulting in poorer scale scores.

Our findings from the SF-36 inventory appears reliable when comparing our results with a recent study conducted on Norwegian CD patients [86]. The current study had almost similar scores (mean and median) as the reference CD sample on the following scales: General Health (~72), Physical Functioning (~96), and Bodily Pain (~73). Notably, our study sample had substantial higher mean and median scores on Vitality, 61.5 and 65.0, respectively. While the mean score in the reference sample was about 45.

### 6.3.2 Clinical Symptoms and Intestinal Histology

Of the 13 symptom scores, only Role-Physical was significantly associated with intestinal histopathology. Whether the lack of association between the other symptom scores was real or due to poor statistical power is uncertain. However, this lack of association between clinical symptoms and histopathology is consistent with findings from other studies [16]. Clinical symptoms may be absent, even when the intestinal mucosa is severely damaged [62]. The literature describes that intestinal recovery may not appear, even on a GFD [103, 104].
Children seem to recover faster and more complete than adults [49], which may indicate that subjects diagnosed in childhood more likely have normal intestinal histology compared to subjects diagnosed in adult age. This is confirmed in a study by Lanzini et al, which found that CD patients diagnosed in adulthood did not show complete mucosal recovery, even on a GFD [103]. Celiac patients diagnosed later in life may have been suffering from CD for many years prior to diagnosis and initiation of the dietary treatment. This may cause intestinal lesions, which become permanent in spite of a strict adherence to the GFD. Lanzini et al. referred to CD patients of adult age when recruiting patients older than 14 years at diagnosis. Mean age at diagnosis in our study sample was 22 (range: 0-57) years old. However, only 10 subjects were classified with histopathological features.

6.3.3 Clinical Symptoms and GFD adherence

Individuals who adhered to the GFD, measured by CDAT score, had fewer symptoms and less health complaints than non–adherent individuals. As regards classic gastrointestinal symptoms, but also concerning more atypical symptoms and health complaints. The current study observed a pattern of better adherence, associated with fewer symptoms, both when adherence was treated as a categorical and a continuous variable. This strengthens the relationship. Our findings were in agreement with a study where similar instrument was used, with poor adherence related to more symptoms [14]. Avoidance of symptoms has been reported as an incentive for being adherent to the GFD [65]. This may sound reasonable, particularly in subjects who are reporting to be sensitive to even small amounts of gluten. More than half of the subjects in the current study reported getting symptoms if they had ingested gluten This implies that the majority had symptom relief as a reason for being adherent to the GFD. This is consistent with the majority of the sample being classified as adherent based on CDAT score.

6.3.4 Nutrient intake in Relation to NNR

The women had an unfavourable intake of the energy-providing nutrients with a large proportion of energy from fat at the expense of carbohydrates and with a poor fatty acid composition. Additionally, folate, iron, vitamin D and dietary fibre were insufficiently covered. The men had a more balanced diet, but with a slightly unfavourable composition of fatty acids. They did not reach the recommended levels of the fat-soluble vitamins, A, D and
E, and folate was below the recommended levels. Both women and men had an intake of phosphate twice that of the recommendations.

In the current study, the dietary intake was compared to the NNR from 2004. Worth mentioning, a revised version will be published in 2012.

The nutrient intake of this sample did not differ considerably from the nutrient intake of the general population [66]. As for the general population, our study sample did not meet the recommended levels of percentage of energy from total fat and saturated fatty acids, which were above the reference levels. Neither were intakes of dietary fibre, vitamin D and folate achieved, corresponding to the general population. Low levels of folate and dietary fibre have been reported in similar studies conducted on Swedish celiac patients [71, 105], additionally a high percentage of energy from fat has been described [67, 68]. Importantly, the reference population, which was used when comparing nutrient intake belongs to the Norkost survey from 1997 [66]. This may be of importance since the dietary pattern in the general population probably has changed over the last 15 years. A new survey (Norkost 3) was conducted in 2011, but the results have not yet been published.

A GFD may cause a limited consumption of carbohydrates and consequently an increased consumption of fat [68]. It is timely to mention that the low carbohydrate-high fat diet seemingly has gained great popularity in the recent year in Norway, considering all the writings in the tabloids, television debates and releases of cookbooks. Therefore, it is appropriate to ask whether this finding is a real tendency in celiac individuals or just a transient phenomenon. Furthermore, there may have been a seasonal influence on diet. Many of the subjects were completing the food recording during the months November and December, which may be a time with increased intake of certain food items in relation to Christmas.

### 6.3.5 Clinical Symptoms and Nutrient Intake

A selection of nutrients regarded as particularly vulnerable in CD were examined in relation to symptom scores. Significant relations between several symptom scores and nutrient intakes were found. Fewer symptoms, measured on three different symptom scales, were associated with higher energy percentage from proteins, while more symptoms were associated with an increased energy percentage from carbohydrates. It can be speculated that these relations can be explained by food choices on a GFD versus a gluten containing diet. The literature has
described that the GFD may result in a reduced intake of carbohydrates [67], likely since many carbohydrate containing food items also contain gluten. Perhaps an increased intake of proteins indicates a diet where carbohydrate rich foods, which contain gluten, are replaced by proteins, as a way of managing a strict GFD. On the opposite, a diet where less protein is consumed may include more carbohydrates including gluten, which consequently triggers symptoms. The lower intake of calcium related to more symptoms could be explained by exclusion of dairy products as a consequence of an acquired lactose intolerance because of intestinal lesions.

6.3.6 Nutritional Status and Intestinal Histology

All the parameters reflecting nutritional status, i.e. BMI, body weight waist-hip ratio and serum levels of micronutrients, were within acceptable levels, implying that the subjects were in good health. No differences were seen between the two Marsh groups as regards these parameters. According to a Finnish study conducted on newly diagnosed CD patients, no differences in anthropometric measures were found between groups with different grades of villous atrophy, but lower levels of folate and serum ferritin was seen in the group with total villous atrophy[22]. Noteworthy, these patients were newly diagnosed, while our sample consisted patients diagnosed for at least 10 years, which may explain why the serum levels were within normal levels in our subjects.

Due to the small sample sizes of the two Marsh groups, it was of no value to make any further division based on gender. Although more correct, as the cut-off values for waist-hip ratio and the reference levels for serum micronutrient levels differs between women and men.

Importantly, the level of education of the study participants was skewed toward higher attainments, which may have implications for nutrient intake and nutritional status in this sample. Socioeconomic differences in dietary intake have been described [106]. Individuals with lower socioeconomic status tend to have a less favourable diet, containing smaller amounts of fruit, vegetables, dietary fibre and some micronutrients [66, 107].


6.4 Methodological Considerations

6.4.1 Design

We conducted a cross-sectional study to obtain information about clinical symptoms and nutrient intake in a sample of the Norwegian celiac population. The strength of this design [108] is that it enabled us to collect data on several variables and to identify issues to be addressed in future research. This is of great value as little research has been conducted on this population. Associations between variables can be explored, but the method lacks the ability to say something about the cause and effect [108]. A shortcoming with our study design was also the lack of a matched control group.

In retrospect, we realised that we should have asked the subjects to bring documentation, which verified the CD diagnosis. Unfortunately, we did not have the capacity to contact the respective hospitals to collect these ourselves. Consequently, we cannot be certain that all of the subjects had CD according to the diagnostic criteria.

6.4.2 Statistics

As our sample size was moderate, outliers may impact the correlation coefficient. For that reason Spearman’s correlation coefficient was used. It is less sensitive to outliers than Pearson’s correlation coefficient. Additionally, the analyses were performed twice, both with all cases included and without outliers, which only slightly affected the results. Removing cases may be incorrect in a small sample, as it may involve a great impact on the correlation. Oppositely, outliers in a small sample may solely be able of showing an apparently dependency between variables. Thus, the associations observed in the current study must be considered with caution. According to Cohen[109], correlation coefficients in the range ± 0.27 to ±0.41, which were significant in our study, represents relationships with small to medium strength.

6.4.3 Assessment of Clinical Symptoms

The Martine Questionnaire

The Martine questionnaire was developed particularly for this study and contained celiac specific symptoms in addition to CSI. MSS has a limitation as it only contains classical
symptoms. However an open-ended question allowed the responders to freely record any symptom. Furthermore, MSS is based on reported symptoms during the last four weeks with only two possible answers (yes or no). Consequently, it may overestimate symptom prevalence, as there may be a lower threshold for responding yes, as there are only two categories, and longer time frame. Worth mentioning, MSS was not intended as a sole unit, separate from the Martine questionnaire. Therefore it may not be as comprehensive as the other symptom assessment instruments. It was reasonable to include methods, which not only assessed celiac specific symptoms as the literature suggests that an increasing number of celiac patients are presenting with atypical symptoms[33, 34]. Hence, the use of additional symptom assessment instruments was crucial. GSRS-IBS records symptoms over the last three days on a Likert scale and each item consists of seven possible answers (no discomfort to very severe discomfort). A strength of GSRS-IBS is that it measures the severity of the complaints in addition to providing the responder with alternative answers. GSRS-IBS is commonly performed by the same subject on two different occasions to measure change in gastrointestinal symptoms. As we only intended to identify symptoms, GSRS-IBS was only performed on one occasion.

**CSI**

CSI has only been conducted in an American celiac population, hence may not be valid in a Norwegian celiac sample. However, the instrument was made in order to assess CD specific symptoms. It was developed by an expert committee comprising gastroenterologists, dieticians, psychologists and CD patients and was additionally reviewed by CD patients in focus groups, which implies a thoroughly work. Leffler et al. suggested that CSI may be a suitable instrument in assessing symptoms across a variety of clinical presentations.

**SHC and SF-36**

SHC and SF-36 are generic i.e. not specific to any age, disease or treatment group and consequently cover a wider area of the health concept. Both SHC and SF-36 have been conducted in samples, representative for the Norwegian population, which allowed us to compare our results with normative data.
6.4.4 Dietary assessments

Validation of the dietary assessment

It seems likely that some under-reporting did occur in our sample, as there was found a deviation between expected and estimated PAL, provided that the subjects were in energy balance. According to an expert report by FAO/WHO/UNU, the PALs of women and men doing light activity are, 1.56 and 1.55, respectively [110]. Whether measured energy intake is representative for habitual intake can be estimated by a cut-off value of 1.35 [96]. This cut-off is below the calculated PAL for our study sample, which implies the opposite. Hence, this suggests that reported energy intake did not differ considerably from the true intake.

Four Day Weighed Food Record

Nutrient intake was calculated from weighed food records conducted over four days. The method puts lots of demand on the subjects and requires that the subjects are motivated [95]. Still, weighed food recording was chosen to obtain a sufficiently detailed record of food intake to be capable of calculating nutrients from absolute intake. A registration period of four days was chosen as it was considered suitable for estimating dietary intake. Additionally, it comprised of three weekdays and one day of the weekend, importantly, to obtain information on habitual intake during the week. Furthermore, a four day time frame was regarded as feasible, which is important, as it has been suggested that motivation declines with increasing number of days. Moreover, the same time frame has been used in similar studies on celiac patients [71, 105]. A strength of this method is that it does not rely on memory, provided that the subjects follow the instruction of recording the foods the time they are consumed [95]. Registration of food eaten outside home may be a challenge with this method, which was expressed by some of the subjects. Under-reporting of energy intake has been commonly described. Another source of error is that individuals deviate from their habitual diet when keeping a dietary record and some may reduce their energy intake during the time of recording. Weighed food recording requires that the subject possess certain numeracy and literacy. Considering the high level of education in the sample, it is unlikely that this has been of any concern.
Nutrient Calculation

The procedure of calculating nutrient intake involves several limitations. The food database, Mat på Data, which was used for calculating nutrient intake, has not been revised recently, which is a shortcoming. The software is based on Matvaretabellen 2006. Consequently, the database lacks many food items, even food items commonly used in most peoples´ diet. Accordingly, the database does not contain many gluten-free products, which obviously were widely used among our study subjects. The program allows new items to be integrated in the database, but this is a labour intensive task. Moreover, many foods do not contain sufficient information about nutrient content, beyond the energy-providing nutrients. This is an important limitation when examining micronutrient intakes.

Noteworthy, the Norwegian Nutrition Society (Norsk Selskap for Ernæring) has recently proclaimed that dieticians, students and others involved in the field of nutrition must put forward a demand that the health authorities must allocate money to upgrade and improve Mat på Data. Additionally, there has been established an activist group on the social forum facebook.

6.4.5 Anthropometric assessments

Hip circumference was measured with clothing. This may underestimate the true ratio between waist and hip. However, after adjustments, the mean ratios for women and men were just slightly changed and still below the cut-off values. Consequently, waist-hip ratio may be a valid measure for nutritional status in our sample.

6.4.6 GFD-adherence

CDAT has only been conducted in a sample of American celiac patients, thus may not be valid in a Norwegian celiac population. The instrument has not been tested against duodenal biopsy histology, but a standardized dietician evaluation was used as gold standard. Additionally, it was evaluated against IgA-TG2 antibody titre. The items in CDAT do not include classic celiac symptoms, hence it may be applicable in a variety of CD patients.

6.4.7 Compliance to the study conduct

A clinical study will always involve unforeseen incidents, which may result in inadequate data on some variables. For instance, one subject did not complete the food recording according to
the instructions, consequently the food record was considered invalid for inclusion in the data analysis. Three food records were never returned. One subject did not respond to the CSI form completely.

6.5 Strengths and Limitations

A major strength of the current study was that clinical symptoms were recorded by five different instruments; MSS, CSI, GSRS-IBS, SHC and SF-36. Together, these instruments provided us with information of a wide spectrum of symptoms and health complaints, not only as regards somatic manifestations, but also concerning the psychological impact of CD.

Data on nutrient intake was collected by a four day weighed food record, which provided a comprehensive picture of nutrient intake of this study sample. This method is regarded as one of the best for that purpose.

Our study sample had a moderate size, which was a constraint when comparing groups of unequal sizes. Additionally, the sample was not randomized, which limits the representativeness and hence the applicability of our findings. A matched control group would have been of great value when interpreting the results. Hence, lack of a suitable reference population was a shortfall. Considering that one of the main objectives of this master thesis was to examine nutrient intake, lack of a sufficient tool for measuring dietary intake was a considerable limitation.

6.6 Clinical Consequences and Implications for Future Research

The observed relation between GFD adherence and clinical symptoms emphasize the importance of keeping a strict GFD. However, managing a strict GFD may not be sufficient, which has been described in the literature [71]. The suboptimal intake of iron, folate, vitamin D and dietary fibre, in particular, and the unfavourable fat distribution in this study sample, implies that individuals with CD treated with the GFD for several years may be in risk of nutrient deficiencies. Considering the inadequate tool utilised for calculating nutrient intake, it can be questioned whether these values represent the true intake of the subjects in this study. Of note, similarities between the study sample and the general Norwegian population,
regarding nutrient intake, may suggest that our study sample did not differ considerable from non-celiac individuals.

Nevertheless, there is most likely a great potential of improving the GFD in terms of making it more balanced, nutritious and palatable. It may be required an extra effort when gluten containing food items are to be replaced by substitutes with similar nutrient content. Analyses of gluten-free foods have revealed that they may not be as nutritious as the corresponding gluten-containing foods [70]. This implies that other food items may be preferable, but knowing what foods should be included in the GFD to make it nutritious requires knowledge. Education of CD patients by trained dieticians and regular follow-up by the health-care system will be crucial to ensure not only a strict GFD adherence, but a nutritious GFD as well.

CELIEN has generated knowledge and hence new questions. Even though this study revealed several statistically significant findings, the results must be considered with caution. Future studies will be required to see if our findings are representative for the total population of Norwegian CD patients.

Research on Norwegian celiac patients regarding clinical symptoms and nutritional status is an uncharted territory, hence many issues should be addressed:

1) CELIEN was restricted to a small sample from Eastern Norway. How CD impacts on individuals with CD from other areas are uncertain, thus need to be explored. An expansion of the current study should comprise a larger sample of CD patients and include individuals from all regions of Norway.

2) The current study implies that individuals with CD have an insufficient nutrient intake and an unfavourable intake of the energy providing nutrients. Whether this can be explained by a poor adherence to the GFD, a poor composition of the diet or of other factors remains to be explored. The impact of dietary supplements on the total nutrient intake and nutritional status is uncertain, and should be examined.

3) Hopefully, this study underlines the urgent need to develop the current food data base, *Mat på Data*, if information on nutrient intake is to be assessed adequately in future research as well as in the clinic.

4) In recent years, food based research has been of major focus in the area of nutrition and consequently the dietary recommendations published in January 2011[111] was
food based. Investigating the GFD in terms of foods instead of nutrients could provide valuable knowledge applicable both in education and in the clinical setting.
7 Conclusion

In the present study we found that our study sample of individuals with CD reported clinical symptoms to a fairly small extent, in terms of severity of the health complaints and how symptoms seemed to impact on health.

There were not found any convincing association between clinical symptoms and intestinal histology. Only Role-Physical (SF-36) differed significantly between the group with intestinal histopathology and the group with no pathological features.

Clinical symptoms and health complaints were reported to a considerable smaller extent in the adherent group compared to the non-adherent group. Significant associations from several symptom scales supported this relation.

The study sample did not have an adequate nutrient intake according to the NNR. Women tended to have an unbalanced intake of the energy providing nutrients with a too high consumption of total fat and saturated fatty acids and consequently a low intake of carbohydrates. Furthermore, iron, folate, vitamin D and dietary fibre were insufficiently covered. The men had a more balanced diet, but with a slightly insufficient intake of mono- and polyunsaturated fatty acids, fat-soluble vitamins and folate.

It was seen a relation between increased percentage of energy from proteins and higher intake of calcium in association with fewer symptoms and less health complaints.

Nutritional status did not differ between groups with intestinal histopathology and normal intestinal histology.
References


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Appendix 1: Advertisement: Invitation to participate in CELIEN

**Cøliakistudien på østlandet**

Invitasjon til deltagelse i prosjekt på Rikshospitalet

-Oppfølging av cøliaki

Høsten 2011 starter et prosjekt ved Rikshospitalet hvor vi skal undersøke hvordan norske cøliakipasienter følger glutenfri kost, samt utvikle et objektivt redskap for å bedømme dette. Personer over 18 år fra østlandsområdet som har hatt diagnostisert cøliaki i mer enn 10 år inviteres til å delta i prosjektet. Dette vil innebære oppfølging med en undersøkelse av hvordan det står til med deg som cøliakipasient. **Med deltakelse vil du:**

1. **Gjennomgå en grundig helsesjekk i forhold til din cøliaki:**
   a. Utfylling av spørreskjemaer
   b. Kostholdsvurdering hos klinisk ernæringsfysiolog på Rikshospitalet
   c. Gastroскопi og blodprøver hos lege på Rikshospitalet
   d. Benmineralmåling og måling av kroppssammensetning

2. **Bidra til at vi kan utvikle bedre redskaper for å følge opp cøliakipasienter i Norge**

Ta kontakt dersom du ønsker mer informasjon og er interessert i å delta.

Med vennlig hilsen

Klinisk ernæringsfysiolog ved Rikshospitalet
Gry Skodje, telefon: 23 07 19 15

Astrid Løvik, telefon: 23 07 19 14

Overlege ved gasroundersøkelse ved Rikshospitalet
Knut Lundin, telefon: 23 07 23 88
Appendix 2: The process of developing the Martine questionnaire

Development of the Martine questionnaire

Dietary habits are strongly dependent of culture. The Martine questionnaire was developed for the purpose of assessing GFD adherence in Norwegian celiac patients. Knowledge was drawn from literature reviews and focus groups, and the development of the questionnaire involved following steps:

Step 1: Literature research

We searched Pubmed for literature using the following search terms: “celiac disease”, “compliance/ adherence”, “gluten-free diet”.

Leffler’s celiac disease assessment instrument [63] and van Hees’ Gluten-free Dietary Habits questionnaire, Coeliac disease, diet stringency and depression (under review: van Hees. N.J.M, van der Does, A.J.W & Giltay, E.J) were used during the preparation of the questionnaire

Step 2: Planning and conducting focus groups

Two focus group sessions were conducted on two consecutive evenings. The aim of the focus groups was to get a better understanding of behaviour in relation to GFD adherence: In this way being able to form questions which also capture not so obvious aspects of GFD.

Thirteen persons with CD were participating in focus groups, six persons in the first session and seven in the last. The participants were mainly recruited through a patient register from OUS, Rikshospitalet. One of the participants was recruited through an announcement at Facebook, and two were acquaintances of the research group. The only criterion for participation was biopsy proven CD.

Before the group discussion started, the participants were thoroughly informed about the aim of the focus group and instructed in how to behave during the session.

A pre-made interview guide sat the frame for the discussion and made sure that important topics were not missed out. We gained a brief instruction in how to carry out a focus group from Focus groups: a practical guide for applied research [112].
The participants in the focus groups were asked to share their experiences, thoughts and opinions in relation to their understanding of what adherence to a GFD means. Barriers to following a GFD, attitudes to a GFD and their view of what influence their adherence were also important topics to discuss. Each session lasted 90 minutes and was audio taped and supplemented with field notes.

**Step 3: Processing knowledge from focus groups and literature and preparing the questionnaire**

The recorded material from the focus group sessions was listened through after the two meetings. Issues that were discussed the most were used in developing the Martine questionnaire.

**Step 4: Pilot study**

A different sample of celiac patients participated in the pilot testing of Martine. Twelve individuals reviewed the questionnaire. It was handed out to persons, functioning as peers to members in NCF, and sent by mail to acquaintances and relatives of the research group. The only criterion for partaking in pilot study was having biopsy proven CD.

The Martine questionnaire was pre-tested in several turns before completion. *The Sample Protocol for Pilot Testing Survey Items* by Rogers was used as guidance for the pilot testing [113]. The participants in the pilot study where asked to be particularly attentive to the following aspects when completing the questionnaire: *understandable, scale adequate, only one response and loaded*. The feedback from the participants and the way we interpreted the completed questionnaires were leading the process of improving the questionnaire. Finally, dieticians experienced with celiac patients read through the questionnaire and suggested changes.
## Appendix 3: The Martine Questionnaire

### BAKGRUNNSINFORMASJON

1. **Fødselsdato:**
   - Dag: [ ]
   - Mnd: [ ]
   - År: [ ]

2. **Kjønn:**
   - [ ] Mann
   - [ ] Kvinne

3. **Nåværende sivil status:**
   - [ ] Gift/samboer
   - [ ] Singel/enselig

4. **Hvor mange er det totalt i husholdningen? [antall]**
   - [ ] (antall) har cølialki.

5. **Høyest fullført utdanning:**
   - [ ] Grunnskole
   - [ ] Vidergående
   - [ ] Høyskole/universitet
   - [ ] Høyskole/universitet 5 år eller mer

6. **Medlemsskap i Norsk cølialkiforening:**
   - [ ] Ja
   - [ ] Nei

7. **Bruker du kun naturlig glutenfrie produkter (uten hvetestivelse)?**
   - [ ] Ja
   - [ ] Nei

8. **Annen matværeallergi:**
   - [ ] Ja
   - [ ] Nei
   - [ ] Yet ikke

9a. **Diagnosetidspunkt for cølialki:**
   - Mnd: [ ]
   - År: [ ]

9b. **Ved hvilket sykehus?**

10. **Tidspunkt for oppstart av glutenfri diett:**
    - Mnd: [ ]
    - År: [ ]
11 a. Har du noen gang avbrutt dietten?  ☐ Ja  ☐ Nei

b. Dersom ja, fyll ut årstall, varighet og årsak for avbrudd/-ene:

Eks. avbrudd i 2001 med varighet 2 mnd. Og 14 dager pga. utenlandsopphold

<table>
<thead>
<tr>
<th>ÅRSTALL</th>
<th>VARIGHET</th>
<th>ÅRSAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ÅR</td>
<td>MND.</td>
<td>DAGER</td>
</tr>
<tr>
<td>2</td>
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<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>ÅRSTALL</th>
<th>VARIGHET</th>
<th>ÅRSAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ÅR</td>
<td>MND.</td>
<td>DAGER</td>
</tr>
</tbody>
</table>
DET GLUTENFRIE KOSTHOLDET

12. De siste 4 ukene har jeg fulgt en glutenfri diet perfekt:
- [ ] Hele tiden
- [ ] Mesteparten av tiden
- [ ] Halvparten av tiden
- [ ] Litt av tiden
- [ ] Ikke i det hele tatt

13. Kryss av for opplevde symptomer de siste 4 ukene, ja eller nei:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Ja</th>
<th>Nei</th>
<th>Symptom</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppblåst mage</td>
<td></td>
<td></td>
<td>Forstoppelse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vektsendring</td>
<td></td>
<td></td>
<td>Magesmerter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luftplagor</td>
<td></td>
<td></td>
<td>Kvalme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaré</td>
<td></td>
<td></td>
<td>Oppkast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trøtthet/slapphet</td>
<td></td>
<td></td>
<td>Hodepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Annet:

-----------------------------------------------

14. Hvor ofte opplever du symptomer?
- [ ] Døglig
- [ ] Ukentlig
- [ ] Månedlig
- [ ] Nøen ganger i året
- [ ] Aldri

15. Dersom du har fått i deg gluten, opplever du symptomer?
- [ ] Alltid
- [ ] Ofte
- [ ] Av og til
- [ ] Sjelden
- [ ] Aldri

16. Hvor ofte får du symptomer hvis du får i deg selv små mengder gluten, for eksempel brødsmuler?
- [ ] Alltid
- [ ] Ofte
- [ ] Av og til
- [ ] Sjelden
- [ ] Aldri
17 a. Kan du smake på glutenholdig mat uten å få symptomer, for eksempel smake på en saus eller ta en bit av en hvetebolle?

☐ Ja  ☐ Nei

b. Hvor mange ganger i året skjer det at du smaker på glutenholdig mat?

☐ Aldri  ☐ 1-2 ganger  ☐ 3-5 ganger  ☐ 6-10 ganger  ☐ Mer enn 10 ganger

18. Hvor mange ganger i løpet av den siste måneden har du spist gluten med viis?

☐ Aldri  ☐ 1-2 ganger  ☐ 3-5 ganger  ☐ 6-10 ganger  ☐ Mer enn 10 ganger

19. Hender det at du spiser gluten uten at du er klar over det (for eksempel glemmer at du ikke kan spise visse matvarer)?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

20. Dersom du er usikker på om en matvare inneholder gluten, hender det at du spiser den likevel?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

21. Dersom du er på ferie, hender det at du avvikler fra den glutenfrie dietten?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

22. Er mat på vei til jobb, skole, reise ("mat i farter"), situasjoner hvor du lettere utsetter deg for glutenholdig mat?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

23. Hvor ofte hender det at du spiser glutenholdig mat for å være høflig eller av hensyn til andre?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

24. Hvor ofte hender det at du spiser gluten for ikke å være "annerledes" og for å unngå spørsmål i sosiale sammenhenger?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
25. Forstår du ingredienslister på produkter?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

26. Hvor ofte sjekker du ingredienslister på produkter du tidligere ikke har brukt?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

27. Hvor ofte sjekker du ingredienslisten til produkter du vanligvis bruker for å kontrollere at de fortsatt er glutenfrie?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

28. Hvor ofte kontrollerer du følgende produkter for gluten?
   a. Kosmetikk (for eksempel smink):
      ☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
      ☐ Bruker ikke
   b. Deodorant og kremer (for eksempel bodylotion, ansiktskrem):
      ☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
      ☐ Bruker ikke
   c. Legemidler:
      ☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
      ☐ Bruker ikke
   d. Kosttønkhud:
      ☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
      ☐ Bruker ikke
   e. Håroprodukter (for eksempel sjampo, stylingprodukter):
      ☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
      ☐ Bruker ikke

29. Unngår du matvarer som kan inneholde spor av gluten?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
30. Klarer du å unngå gluten i uforutsette situasjoner?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

31. Hender det at du avvikler fra dieten i situasjoner dør det er krevende å finne glutenfrie alternativer?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

32. Sørger du for at andre som skal lage mat til deg vet tilstrekkelig om celiaki?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

33. Unngår du at mat kommer i kontakt med glutenholdige matvarer eller redskaper?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri

34. Unngår du glutenholdig melstøv ved matlaging?

☐ Alltid  ☐ Ofte  ☐ Av og til  ☐ Sjelden  ☐ Aldri
CØLIAKI I HVERDAGEN

35. Kostnader på glutenfri mat gjør det vanskelig for meg å holde meg til en glutenfri diett:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

36. Kvaliteten (ismak, konsistens, sunnhet) på glutenfri mat gjør det vanskelig for meg å holde meg til en glutenfri diett:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

37. Ett er mening er merkingen av glutenfrie matvarer i Norge god nok.
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

38. Det er vanskelig å få tak i glutenfri mat:
a. I butikken:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

b. På restaurant/ café:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

39. Ett er mening er det en utfordring å finne glutenfrie alternativer i hverdagen:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

40. Jeg føler jeg har god nok kunnskap til å ta veloverveide beslutninger i forhold til å mestre den glutenfrie dietten:
☐ Enig  ☐ Delvis enig  ☐ Usikker  ☐ Delvis uenig  ☐ Uenig

41. Hvor får du informasjon om cøliaki og glutenfri kost? Flere kryss mulig:
☐ Fastlege  ☐ Gastroenterolog  ☐ Klinisk ernæringsfysiolog  ☐ Norsk cøliakforer
☐ Forskningsartikler  ☐ Media  ☐ Bøker  ☐ Internett  ☐ Annet

........................................................................................................................................................................
42. Jeg føler at helsepersonells oppfølging av meg som cæliakasjent er/har vært tilstrekkelig:
   □ Enig   □ Delvis enig   □ Usikker   □ Delvis uenig   □ Uenig

43. Hvilke kilder kunne du tenke deg mer informasjon fra? Flere kryss mulig:
   □ Fastlege   □ Gastroenterolog   □ Klinisk emøringsfysiolog   □ Norsk cæliakasjeforening
   □ Ønsker ikke mer informasjon   □ Annet:
   ........................................................................................................

44. Er det informasjon du ville hatt mer av? Flere kryss mulig:
   □ Oppskrifter   □ Prosesser i tarmen   □ Helsekonsekvenser   □ Ingredienser/matmerking
   □ Ønsker ikke mer informasjon   □ Annet:
   ........................................................................................................

45. Det har vært utfordrende å følge en glutenfri diet de siste 4 ukene:
   □ Enig   □ Delvis enig   □ Usikker   □ Delvis uenig   □ Uenig

46. I hvilken grad vil du si den glutenfrie kosten er viktig for helsen din?
   □ Viktig   □ Litt viktig   □ Usikker   □ Litt uviktig   □ Ikke viktig

47. Hvor viktig er støtte fra for eksempel Norsk cæliakasjeforening, venner, familie, kolleger i forhold til hvordan du mester den glutenfrie dietten?
   □ Viktig   □ Litt viktig   □ Usikker   □ Litt uviktig   □ Ikke viktig
48. Kan noen av disse situasjonene være utfordrende i forhold til å holde en glutenfri diett?
   a. Reise, innenlands:
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig
   a. Reise, utenlands:
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig
   b. Sosiale sammenkomster med familien (innenfor samme husholdning):
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig
   c. Sosiale sammenkomster med stor familien (for eksempel i juleselskaper):
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig
   a. Sosiale sammenkomster utenfor familien:
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig
   d. Religiøse seremonier:
      □ Enig □ Delvis enig □ Usikker □ Delvis uenig □ Uenig □ Deltar ikke
   e. Andre situasjoner: .................................................................

49. Kryss av for faktorer som påvirker hvordan du følger en glutenfri kost, ja eller nei:

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>
   Samvittighet | □ | □ | | |
   Lengstidskonsekvenser | □ | □ | □ | □ |
   Smak på glutenfrie produkter | □ | □ | □ | □ |
   Følelse av å skille seg ut | □ | □ | □ | □ |

Annet: ........................................................................................................

50. Hvordan vurderer du helsen din i forhold til ikke-cøltakere?
    □ Mye bedre  □ Litt bedre  □ Like god  □ Litt dårligere  □ Mye dårligere
## Appendix 4: Celiac Symptom Index (CSI)

<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Har du vært plaget med smerte eller ubehag i øvre eller sentrale del av magen i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>2. Har du vært plaget med kvalme i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>3. Har du vært plaget med rumling i magen i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>4. Har du vært oppblåst i magen i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>5. Har du vært plaget med diaré i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>6. Har du hatt følelsen av ufullstendig tomning når du har vært på toalett i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>7. Har du vært plaget med sultsmmer i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>8. Har du vært plaget av mangelende overskudd i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>9. Har du vært plaget av hodepine i løpet av de siste 4 ukene?</td>
<td>Ikne i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>10. Har du føyet på spesiell mat i løpet av de siste 4 ukene?</td>
<td>Ikne i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>11. Har du hatt manglende matlyst i løpet av de siste 4 ukene?</td>
<td>Ikne i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>12. Relatert til din celiaki, hvordan er helsen din?</td>
<td>Umerket</td>
<td>God</td>
<td>Ganske god</td>
<td>Dårlig</td>
<td>Meget dårlig</td>
</tr>
<tr>
<td>14. Hvor mye fysisk smerte har du hatt i løpet av de siste 4 ukene?</td>
<td>Ingening</td>
<td>Litt</td>
<td>En del</td>
<td>Ganske mye</td>
<td>Veldig mye</td>
</tr>
<tr>
<td>15. Jeg har det (helvemessig) bra</td>
<td>Sterkt enig</td>
<td>Noe enig</td>
<td>Verken enig eller uenig</td>
<td>Noe uenig</td>
<td>Sterkt uenig</td>
</tr>
<tr>
<td>16. Jeg er like frisk som hvem som helst andre jeg kjener</td>
<td>Sterkt enig</td>
<td>Noe enig</td>
<td>Verken enig eller uenig</td>
<td>Noe uenig</td>
<td>Sterkt uenig</td>
</tr>
</tbody>
</table>
Appendix 5: Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS)

The Gastrointestinal Symptom Rating Scale (GSRS)
Irritable Bowel Syndrome (IBS)-Versjon

Les dette først:
Undersøkelsen inneholder spørsmål om hvordan du har følt deg og hvordan du har hatt det de 3 siste dager. Sett kryss (X) ved det alternativet som passer best på deg og din situasjon.

1. Har du i løpet av de siste tre dagene vært plaget av magesmerter?
   - □ Ingen plager i det hele tatt
   - □ Ubeøydelige plager
   - □ Milde plager
   - □ Moderate plager
   - □ Ganske alvorlige plager
   - □ Alvorlige plager
   - □ Meget alvorlige plager

2. Har du i løpet av de siste tre dagene vært plaget av smertem eller ubehag i magen som gir seg når du har hatt avføring?
   - □ Ingen plager i det hele tatt
   - □ Ubeøydelige plager
   - □ Milde plager
   - □ Moderate plager
   - □ Ganske alvorlige plager
   - □ Alvorlige plager
   - □ Meget alvorlige plager
3. Har du i løpet av de siste tre dagene vært plaget av OPPBLÅSTHET?

- Ingen plager i det hele tatt
- Ubenyttelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
- Alvorlige plager
- Meget alvorlige plager

4. Har du i løpet av de siste tre dagene vært plaget av LUFTAVGANG?

- Ingen plager i det hele tatt
- Ubenyttelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
- Alvorlige plager
- Meget alvorlige plager

5. Har du i løpet av de siste tre dagene vært plaget av FORSTOPPELSE (problemer med å termme tarmen)?

- Ingen plager i det hele tatt
- Ubenyttelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
- Alvorlige plager
- Meget alvorlige plager
6. Har du i løpet av de siste tre dagene vært plaget av DIARRÉ (hyppig avfering)?

☐ Ingen plager i det hele tatt
☐ Ubetydelige plager
☐ Milde plager
☐ Moderate plager
☐ Ganske alvorlige plager
☐ Alvorlige plager
☐ Meget alvorlige plager

7. Har du i løpet av de siste tre dagene vært plaget av LØS AVFØRING?

☐ Ingen plager i det hele tatt
☐ Ubetydelige plager
☐ Milde plager
☐ Moderate plager
☐ Ganske alvorlige plager
☐ Alvorlige plager
☐ Meget alvorlige plager

8. Har du i løpet av de siste tre dagene vært plaget av HARD AVFØRING?

☐ Ingen plager i det hele tatt
☐ Ubetydelige plager
☐ Milde plager
☐ Moderate plager
☐ Ganske alvorlige plager
☐ Alvorlige plager
☐ Meget alvorlige plager
9. Har du i løpet av de siste tre dagene vært plaget av TVINGENDE AVFØRINGSBEHOV (plutselig behov for å gå på toalettet for å temme tarmen)?

- Ingen plager i det hele tatt
- Ubetydelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
- Alvorlige plager
- Meget alvorlige plager

10. Har du i løpet av de siste tre dagene vært plaget av en FØLELSE AV UFULLSTENDIG TØMNING AV TARMEN ETTER AVFØRING?

- Ingen plager i det hele tatt
- Ubetydelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
- Alvorlige plager
- Meget alvorlige plager

11. Har du i løpet av de siste tre dagene vært plaget av at du FØLER DEG METT LIKE ETTER AT DU HAR BEGYNNT PÅ ET MÅL? TID?

- Ingen plager i det hele tatt
- Ubetydelige plager
- Milde plager
- Moderate plager
- Ganske alvorlige plager
12. Har du i løpet av de siste tre dagene vært plaget av at du FØLER DEG METT SELV LENGE ETTER AT DU ER FERDIG MED Å SPISE?

- Ingen plagør i det hele tatt
- Ubetydelige plagør
- Milde plagør
- Moderate plagør
- Ganske alvorlige plagør
- Alvorlige plagør
- Meget alvorlige plagør

13. Har du i løpet av de siste tre dagene vært plaget av at MAGEN ER SYNLIG OPPBLÅST?

- Ingen plagør i det hele tatt
- Ubetydelige plagør
- Milde plagør
- Moderate plagør
- Ganske alvorlige plagør
- Alvorlige plagør
- Meget alvorlige plagør

KONTROLLER AT ALLE SPØRSMÅLENE ER BESVART!

TAKK FOR DIN MEDVIRKNING.
### Appendix 6: Subjective Health Complaints (SHC)

<table>
<thead>
<tr>
<th>Nedenfor nevnes noen alminnelige helseproblemer</th>
<th>Ikke plaget</th>
<th>Litt plaget</th>
<th>Endel plaget</th>
<th>Alvorlig plaget</th>
</tr>
</thead>
<tbody>
<tr>
<td>(sett ind ringt tallet som passer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.   Forkjølelse, influensa</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2.   Hoiste, bronkitt</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.   Astma</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4.   Hodepine</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5.   Nakkenmerter</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6.   Smerter overst i ryggen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7.   Smerter i kroppen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8.   Smerter i armene</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9.   Smerter i sjukene</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10.  Mignene</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11.  Hjertebank, ekstralag</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12.  Bryttsmerter</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>13.  Pastenærke</td>
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<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14.  Smerter i fottene ved anstrengelser</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>15.  Sore oppsatt, skalhasten</td>
<td>0</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16.  Sog eller sve i magen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17.  Magaktaer, magesår</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>18.  Magesnip</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>19.  «Luftplager»</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>20.  Los avføying, dåré</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>21.  Forstoppelse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>22.  Eksem</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>23.  Allergi</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>24.  Hetetokter</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>25.  Sovnproblemer</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>26.  Teethtet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>27.  Svinnelighet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>28.  Angst</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>29.  Nedtrykt, depresjon</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Tillegsoppsimal dersom du har angitt flere helseproblemer:
Hvilket av disse problemene har vært mest plagesom for deg siste 3 dager? (skriv navnet på helseproblemet)

IDKode _______________________________
Appendix 7: Short Form-36 (SF-36)


SF-36

1. Stort sett vil du si at din helse er:
   - Øverkert
   - Meget god
   - God
   - Nokså god
   - Dårlig

2. Sammenlignet med for et år siden, hvordan vil du si at din helse stort sett er nå?
   - Mye bedre nå enn for et år siden
   - Litt bedre nå enn for et år siden
   - Omtrent det samme som for et år siden
   - Litt dårligere nå enn for et år siden
   - Mye dårligere nå enn for et år siden

3. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

A. Anstrengende aktiviteter som å lepe, løfte tunge gjenstander, delta i anstrengende idrett...
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.

B. Moderate aktiviteter som å lyyte et bord, støvle, få en tur eller drive med hagearbeid
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.

C. Løfte eller bære en handledkurv
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.

D. Gå opp trappen flere steg
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.

E. Gå opp trappen en etasje
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.

F. Bøye deg eller sitte på huk
   - Ja, begrenser meg mye.
   - Ja, begrenser meg litt.
   - Nei, begrenser meg ikke i det hele tatt.
G. Går mer enn 10 kilometer
   □ Ja, begrenser meg mye. □ Ja, begrenser meg litt. □ Nei, begrenser meg ikke i det hele tatt.

H. Går noen hundre meter
   □ Ja, begrenser meg mye. □ Ja, begrenser meg litt. □ Nei, begrenser meg ikke i det hele tatt.

I. Går hundre meter
   □ Ja, begrenser meg mye. □ Ja, begrenser meg litt. □ Nei, begrenser meg ikke i det hele tatt.

J. Vaske deg eller kle på deg
   □ Ja, begrenser meg mye. □ Ja, begrenser meg litt. □ Nei, begrenser meg ikke i det hele tatt.

4. I løpet av de siste fire ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

   A. Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?
      □ Ja □ Nei

   B. Har du utrettet mindre enn du hadde ønsket?
      □ Ja □ Nei

   C. Har du vært hindret i visse typer arbeid eller andre aktiviteter?
      □ Ja □ Nei

   D. Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter (f.eks. ford i det krevede ekstra anstrengelser)?
      □ Ja □ Nei

5. I løpet av de siste fire ukene, har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (f.eks. ford i du har følt deg depressert eller engstelig)?

   A. Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter?
      □ Ja □ Nei

   B. Har du utrettet mindre enn du hadde ønsket?
      □ Ja □ Nei

   C. Har du ikke arbeidet eller utført andre aktiviteter like nøye som vanlig?
      □ Ja □ Nei

6. I løpet av de siste fire ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, nabover eller foreninger?

   □ Ikke i det hele tatt □ Litt □ Endel □ Mye □ Svært mye
7. Hvor sterke kroppslige smøter har du hatt i løpet av de siste fire ukene?

- ingen
- Moderete
- Meget svake
- Sterke
- Svake
- Meget sterke

8. I løpet av de siste fire ukene, hvor mye har smøter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemme og husarbeid)?

- hele tiden
- litt av tiden
- ikke i det hele tatt
- endel av tiden

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det den siste måneden. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av den siste måneden har du:

A. Felt deg full av tiltakslys?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

B. Felt deg veldig nervøs?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

C. Vært så langt nede at ingen ting har kunnet muntre deg opp?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

D. Felt deg rolig og harmonisk?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

E. Hatt mye overskudd?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

F. Felt deg nedenfor og trist?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

G. Felt deg silten?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

H. Felt deg glad?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt

I. Felt deg trett?

- hele tiden
- endel av tiden
- nesten hele tiden
- litt av tiden
- mye av tiden
- ikke i det hele tatt
J. løpet av den siste uken, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

- [ ] Helo tiden
- [ ] Endel av tiden
- [ ] Nesten hele tiden
- [ ] Litt av tiden
- [ ] Mye av tiden
- [ ] Ikke i det hele tatt

10. Hvor RIKTIG eller GÅLTER hver av de følgende påstander for deg?

<table>
<thead>
<tr>
<th>Påstand</th>
<th>Helt riktig</th>
<th>Delvis</th>
<th>Vot ikke</th>
<th>Delvis galt</th>
<th>Helt galt</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Det virker som om jeg blir lettere syk enn andre</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>B) Jeg er like frisk som de fleste jeg kjenner</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>C) Jeg forventer at min helse vil bli dårligere</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>D) Min helse er utmerket</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
Appendix 8: Four day weighed food record: Instructions and food diary

Dagbok for 4-dagers veid kostregistrering       Veiledning

Vei og skriv ned alt du spiser i 4 påfølgende dager. Vi vil at du skal gjøre
registreringen dagene tirsdag til og med fredag, og starter opp førstkommende
tirsdag.

Angi mattype og drikke nøyaktig. Se eksempelet nedenfor. Lager du eget brød eller
anret bakverk, legger du ved oppskriften og skriver ned antall brød/mengde av
ferdigstekt bakverk. Dersom du ikke spiser hele matmengde du har veid opp, trekker
du fra mengden du ikke har spist. Det samme gjør du dersom du har spist eple,
banan eller lignende (trekker fra vekten til bananskall og epieskrott).

Veilingen:
1. Slå på vekten.
3. Vei første matvare. Notér vekten. Tarér
4. Legg på ny matvare. Noter vekten. Tarér. osv

Husk å oppgi:   Type brød, knækkebrød og kjeks
                     Type matfett (Meiersmør. Soft flora, osv)
                     Type pålegg: hellet, lettere, lettprosent
                     Tilberedning av maten (stekt, kot, grillet, panert, osv)
                     Tilbehør til maten (saus, dressing, ketchup, lyttebærssyltetøy,
sukker, fiske, mek, osv)
                     Det du spiser mellom måltidene!

Forsøk å spise som vanlig de dagene du registrerer matinnakket!
Bruk et ark for hver dag og en linje for hver matvare. Skriv på baksiden av arket om
nødvendig. Det er viktig at dette blir gjort riktig, så dersom det oppstår noen
problemer i løpet av registreringsperioden, ikke nøl med å ta kontakt!

Tine Nybråten Tjønsø, mob.: 48 15 81 50
Marie Wegge Nilsen, mob. 91 65 11 92
## Dagbok for 4-dagers veid kostregistrering

### Eksempel:

<table>
<thead>
<tr>
<th>Kl</th>
<th>Matvare</th>
<th>Veid matvare, g: rå</th>
<th>Veid matvare, g: tilberedt</th>
<th>Tillægning/oppskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td>0730</td>
<td>2 brødskiver hjemmebakt glutenfritt havrebrød</td>
<td>60</td>
<td>So oppskrift på baksiden av arket →</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Margarin Vita hjertego lett</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lettmelk Tine 1,5 g fett</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 stekt egg</td>
<td>98</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ts flytende Melange</td>
<td>5</td>
<td>Ved steking av 1egg</td>
<td></td>
</tr>
<tr>
<td>1130</td>
<td>1 porsjon potet-purresuppe</td>
<td>270</td>
<td>So oppskrift på baksiden av arket →</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vann</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>½ banan veid uten skall</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1600</td>
<td>2 kotte poteter uten skall</td>
<td>130</td>
<td>u/skall 122 g</td>
<td>Koko med skall</td>
</tr>
<tr>
<td></td>
<td>1 laksefilet</td>
<td>164</td>
<td>Ovnslakt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Purre</td>
<td>10</td>
<td>Ovnslakt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sukkerroter</td>
<td>33</td>
<td>Ovnslakt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blomkål</td>
<td>78</td>
<td>Ovnslakt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lettreomme 10 % fett</td>
<td>33</td>
<td>Sør dressing/saus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vann</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapsole 1 ss</td>
<td>15</td>
<td>Til ovnsbakingen</td>
<td></td>
</tr>
</tbody>
</table>

### Oppskrift på hjemmebakt brød: 1 brød veier 580 g ferdigstekt

- ½ pk gjær
- 5 dl vann
- ½ dl soyaolje
- 1 ts salt
- 2 dl lettkoke havregryn (ren havre)
- 1 dl laksfrø
- 1 pk (500 g) Semper grøv mix
- naturlig glutenfri

### Oppskrift på potet-purresuppe: Totalen veide 1155 g ferdig tilberedt

- 1 fede hvitløk
- 1 lak
- 350 g skrelte poteter
- 1 middels stor purre
- 7 dl vann
- 1 ½ baljongterming
- ½ ts salt
- 3 ss lettmelk
Dagbok for 4-dagers veid kostregistrering  

Dag 1

Dato: ..............................

<table>
<thead>
<tr>
<th>Kl</th>
<th>Matvare</th>
<th>Veid matvare g:</th>
<th>Tillaging/oppskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rå vare</td>
<td>tilberedt</td>
</tr>
</tbody>
</table>

I ommer.
### Dagbok for 4-dagers veid kostregistrering

**Dag 2**

**Dato:** ..................

<table>
<thead>
<tr>
<th>Kl</th>
<th>Matvare</th>
<th>Veid matvare, g:</th>
<th>Tillaging/oppskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rå vare</td>
<td>tilberedt</td>
</tr>
</tbody>
</table>

IDummer.
Dagbok for 4-dagers veid kostregistrering  

Dag 3

Dato: ........................................

<table>
<thead>
<tr>
<th>Kl</th>
<th>Matvare</th>
<th>Veid matvare, g:</th>
<th>Tillaging/oppskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rå vare</td>
<td>tilberedt</td>
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</table>

IDummer.
Dagbok for 4-dagers veid kostregistrering  

Dag 4  

<table>
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<tr>
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<th>Tillaging/oppskrift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rå vare</td>
<td>tilberedt</td>
</tr>
</tbody>
</table>

IDnummer:
Appendix 9: Celiac Dietary Adherence Test (CDAT)

CDAT
Glutenfri kost

Sett ring rundt svaralternativet som passer best:

<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Har du vært plaget med manglende overskudd i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>2. Har du vært plaget med hodepine i løpet av de siste 4 ukene?</td>
<td>Ikke i det hele tatt</td>
<td>Litt av tiden</td>
<td>En del av tiden</td>
<td>Mesteparten av tiden</td>
<td>Hele tiden</td>
</tr>
<tr>
<td>3. Det er mulig for meg å spise glutenfritt når jeg spiser borte</td>
<td>Sterkt enig</td>
<td>Noe enig</td>
<td>Verken enig eller uenig</td>
<td>Noe uenig</td>
<td>Sterkt uenig</td>
</tr>
<tr>
<td>4. Før jeg gjør noe vurderer jeg nøyve konsekvensene</td>
<td>Sterkt enig</td>
<td>Noe enig</td>
<td>Verken enig eller uenig</td>
<td>Noe uenig</td>
<td>Sterkt uenig</td>
</tr>
<tr>
<td>5. Jeg anser <strong>ikke</strong> meg selv som mislykket</td>
<td>Sterkt enig</td>
<td>Noe enig</td>
<td>Verken enig eller uenig</td>
<td>Noe uenig</td>
<td>Sterkt uenig</td>
</tr>
<tr>
<td>6. Hvor viktig er uhell med gluteninntak for helsen din?</td>
<td>Veldig viktig</td>
<td>Ganske viktig</td>
<td>Nøytral/usikker</td>
<td>Litt viktig</td>
<td>Ikke viktig i det hele tatt</td>
</tr>
<tr>
<td>7. Hvor mange ganger har du spist glutenholdig mat med vilje i løpet av de siste 4 ukene?</td>
<td>0 (aldri)</td>
<td>1-2 ganger</td>
<td>3-5 ganger</td>
<td>6-10 ganger</td>
<td>Mer enn 10 ganger</td>
</tr>
</tbody>
</table>
Appendix 10: Approval from the Regional Ethic Committee

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Klinisk ernæringsfysiolog Gry Irene Skodje
Oslo universitetssykehus HF
Rikshospitalet
0424 Oslo

Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst A (REK Sør-Øst A)
Postboks 1130 Blidern
NO-0318 Oslo

Telefon: 23 84 46 66

Dato: 24.03.2011
Døres ref.: 2011/468a

2011/468a Compliances av glattefri kost

Prosjektleder: Klinisk ernæringsfysiolog Gry Irene Skodje
Forskningsansvarlig: Oslo universitetssykehus HF

Det innhentes en rekke helseopplysninger som blodprøver, næringsinnmat og en symptomregisterering. Videre vil man kartlegge compliance. Prosjektet vil utvikle standarder for gradering av compliance i denne pasientgruppen, noe som ikke finnes fra før.

Det vil innhentes informert samtykke fra deltakerne.

Som ulempe angis 3-dagers registrering av matintakt og besøk på Rikshospitalet.

Fordelene vil være at dersom man finner manglende compliance hos denne gruppen, vil det iverksettes tiltak (hvile!), og resultatene vil være nyttige for industrien.

Data vil håndteres avidentifisert siden materialet skal benyttes til studenterbeidere fremover.

Komiteens finner ikke å kunne godkjenne prosjektet av følgende grunner:

- Det framgår ikke hvordan man vil måle compliance i denne studien. I informasjonsskrivet er prosjektet kalt "mekanismerne for celiakt" uten at dette er forklart.


- Det er ikke samsvar mellom søknad, prosjektbeskrivelse og informasjon. Det er uklart hva som skal gjøres.

Vedtak:
På grunnlag av de ovenfor anførte merknadene kan ikke komiteen godkjenne prosjektet slik det er framlagt. Det må eventuelt lages en ny søknad.
Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK Sørøst A. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § '29.

Vennligst oppgi vårt saksnummer/referansenummer i korrespondansen.

Med vennlig hilsen

Gunnar Nicolaysen (sign)
Professor
Ledige

Jørgen Harding
Komitésekretær

Kopi: Oslo universitetssykehus HF. oushfgodkjenning@ous-hf.no
**Prosjektleder:** Gry Irene Skodje

**Forskningsansvarlig:** Oslo universitetssykehus ved øverste ledelse og Klinikk for spesialisert medisin og kirurgi ved ledelsen

Vi viser til e-postkorrespondanse 05.07.11 samt innsendt skjema for tilbakemelding på komiteens vedtak 22.08.11. Følgende vedlegg er sendt komiteen:

- Revidert informasjonskriv
- Invitasjon til deltakelse i studie
- Revidert forskningsprotokoll

Komiteen vurderte prosjektet første gang i møte 08.06.11 og ba om endringer i prosjektet på følgende punkter:

- Det er ukjent om det faktisk er biobank med meldingsnr 840 i Biobankregisteret som skal benyttes i studien eller om det skal opprettes en ny biobank.
- Det står beskrevet at gastroskopisk ikke er forbundet med risiko. Selv om risikoen er svært liten, er det er liten risiko forbundet med undersøkelsen som bør nevnes i informasjonskrivet.
- Kontaktinformasjon for spørsmål til prosjektet eller for å trekke seg, bør det også være et direktenummer til kliniken som er ansvarlig for studien telefon og en person i tillegg (to personer) til det som er angitt i søknaden.
- Komiteen observerer at det står i informasjonskrivet, at pasienters kostregistrering må inkludere en helligdag. Komiteen regner med at det dreier seg om fire påfølgende dager.
- Komiteen ba om at stedfortredende samtykke tas ut av informasjonskrivet, da det bare skal inkluderes samtykkekompetente personer i studien.

Det er sendt inn informasjon om at man skal benytte eksisterende biobank i prosjektet. Biobanken >Cytofinnetverket ved celiak - underprosjekt av Mekanismerne for celiak studert på vevsprøver fra
tynntarmen» (s-97201) som skal benyttes.

Prosjektleder har sendt inn revidert informasjonsskriv hvor komiteens merknader er innarbeidet.

De omsøkte prosjektendringene dreier seg om at det vil bli målt benmineralitetthet og kroppssammensetning hos alle deltakerne i prosjektet ved andre besøk på Rikshospitalet. Metoden er DXA (Dual-emission X-ray absorptiometry) og utføres på endokrinologisk dagenhet. Metoden er ikke forbundet med ubehag eller risiko. Det er en meget svak stråledose pasienten blir utsatt for. Undersøkelsen innebærer minimal ekstra belastning for deltaker i forhold til hva de skal gjennom.

Forskningsetisk vurdering

Komiteens leder Stein Opjordsmoen Iller har på delegert fullmakt vurdert både tilbakemelding og endringsmelding.

REK sør-øst B godkjener har vurdert revidert informasjonsskriv til å være tilfredsstillende innarbeidelse av komiteens merknader til informasjonsskrivet.

REK sør-øst B har ingen forskningsetiske innvendinger til at prosjektet gjennomføres slik det nå foreligger med innarbeidelse av de her omtalte endringene.

Vedtak

Komiteen har vurdert tilbakemelding og søknad om endring. Komiteen godkjener prosjektet slik det nå foreligger med hjemmel i helseforskningsloven § 10.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, med de innarbeidelsene av endringer komiteen har fått tilsendt som beskrevet i dette vedtaksbrevet, samt de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema senest et halvt år etter prosjektslutt, fritt helseforskningsloven § 12.


Vi ber om at alle henvendelser sendes inn via vår sakportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,
Stein Opjordsmoen Ilner (sign.)
professor dr. med
komiteens leder

Katrine Ore
komitésekretær/rådgiver REK sør-øst B.

Kopi til: p.m.sandset@medisin.uio.no
## Appendix 11: Addition to Results: Nutrient intake compared to NNR, total sample.

Nutrient intake compared to NNR\(^a\)  Mean (SD)\(^b\) and median (Q\(_1\), Q\(_3\))\(^c\). n=55.

<table>
<thead>
<tr>
<th></th>
<th>The Celiac Study in Eastern Norway, 2012</th>
<th>NNR(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)(^b)  Median (Q(_1), Q(_3))(^c)</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Macronutrients, (E%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>39 (9.8)</td>
<td>39 (31, 46)</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>14 (4.3)</td>
<td>13 (10, 17)</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>13 (4.7)</td>
<td>12 (9, 15)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>6 (3.4)</td>
<td>6 (4, 8)</td>
</tr>
<tr>
<td>Trans-fatty acids</td>
<td>&lt;1 (0.5)</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>Protein</td>
<td>17 (3.5)</td>
<td>16 (14, 19)</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>43 (11)</td>
<td>41 (37, 50)</td>
</tr>
<tr>
<td>Sugar</td>
<td>6 (4)</td>
<td>6 (2, 8)</td>
</tr>
<tr>
<td>Dietary fibre (g)</td>
<td>23 (10)</td>
<td>21 (15, 27)</td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A (RE)(^d)</td>
<td>968 (687)</td>
<td>787 (442, 1279)</td>
</tr>
<tr>
<td>Vitamin D (µg)</td>
<td>7.8 (8.6)</td>
<td>5.4 (2.7, 10.5)</td>
</tr>
<tr>
<td>Vitamin E (α-TE)(^e)</td>
<td>21 (54)</td>
<td>11 (6.3, 17)</td>
</tr>
<tr>
<td>Thiamine (mg)</td>
<td>1.4 (0.9)</td>
<td>1.1 (0.9, 1.5)</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>1.8 (1.1)</td>
<td>1.53 (1.1, 2.1)</td>
</tr>
<tr>
<td>Niacin (NE)(^f)</td>
<td>32 (12)</td>
<td>29 (24, 38)</td>
</tr>
<tr>
<td>B(_6) (mg)</td>
<td>2.1 (2.1)</td>
<td>1.7 (1.2, 2.1)</td>
</tr>
<tr>
<td>Folate (µg)</td>
<td>272 (142)</td>
<td>228 (161, 343)</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>176 (195)</td>
<td>119 (77, 196)</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>856 (370)</td>
<td>827 (595, 1052)</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>1395 (460)</td>
<td>1330 (1111, 1607)</td>
</tr>
<tr>
<td>Potassium (g)</td>
<td>3.2 (1.1)</td>
<td>3.0 (2.5, 3.7)</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>17 (38)</td>
<td>10 (7, 13)</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>10 (4.4)</td>
<td>9 (7, 12)</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>56 (32)</td>
<td>47 (36, 63)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>318 (150)</td>
<td>294 (232, 378)</td>
</tr>
</tbody>
</table>

\(^a\)The values are based on a reference group of females, 31-60 years.
\(^b\)SD, standard deviation
\(^c\)Q\(_1\) 25\(^{th\} \text{percentile, Q}_3 75\(^{th\} \text{percentile}
\(^d\)RE, Retinol equivalents; 1 retinol equivalent (RE)=1µg retinol=12 µg β-carotene
\(^e\)α-TE, α-tocopherol equivalents; 1 α-tocopherol equivalent =1mg RRR- α-tocopherol
## Appendix 12

Serum level of micronutrients for women and men. Median (Q₁,Q₃)\(^a\) and mean (SD)\(^b\).

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Iron</td>
<td>43</td>
<td>18 (21, 15)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>44</td>
<td>13.8 (13.2, 14.0)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>43</td>
<td>63 (39, 100)</td>
</tr>
<tr>
<td>Transferrin</td>
<td>43</td>
<td>2.7 (2.4, 3)</td>
</tr>
<tr>
<td>Transferrin sat.(^c)</td>
<td>43</td>
<td>0.27 (0.24, 0.33)</td>
</tr>
<tr>
<td>Folate</td>
<td>44</td>
<td>20.5 (17, 29.8)</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>44</td>
<td>367 (291, 514)</td>
</tr>
<tr>
<td>Vitamin B₉</td>
<td>36</td>
<td>55 (35, 81)</td>
</tr>
<tr>
<td>Homocystein</td>
<td>44</td>
<td>9 (7, 11)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>43</td>
<td>5.1 (4.6, 5.6)</td>
</tr>
<tr>
<td>LDL-C(^d)</td>
<td>43</td>
<td>2.9 (2.4, 3.6)</td>
</tr>
<tr>
<td>HDL-C(^e)</td>
<td>43</td>
<td>1.8 (1.6, 2.0)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>43</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>44</td>
<td>1.7 (1.4, 2)</td>
</tr>
<tr>
<td>Calcium</td>
<td>44</td>
<td>2.3 (2.2, 2.3)</td>
</tr>
<tr>
<td>Adj. calcium(^f)</td>
<td>37</td>
<td>1.21 (1.20, 1.24)</td>
</tr>
<tr>
<td>25-OH-Vit.D(^g)</td>
<td>40</td>
<td>70 (60, 84)</td>
</tr>
<tr>
<td>1,25-OH-Vit.D(^h)</td>
<td>40</td>
<td>123 (104, 151)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>43</td>
<td>0.81 (0.76, 0.85)</td>
</tr>
<tr>
<td>Selenium</td>
<td>33</td>
<td>1.1 (0.9, 1.2)</td>
</tr>
<tr>
<td>Zinc</td>
<td>42</td>
<td>14 (13, 15)</td>
</tr>
</tbody>
</table>

\(^{a}\) Q₂₅\(^a\) percentile, Q₇₅\(^a\) percentile  
\(^{b}\) SD, standard deviation  
\(^{c}\) Transferrin saturation  
\(^{d}\) Low density lipoprotein cholesterol  
\(^{e}\) High density lipoprotein cholesterol  
\(^{f}\) Albumin adjusted calcium  
\(^{g}\) 25-dihydroxy vitamin D  
\(^{h}\) 1,25-dihydroxy vitamin D