

Nutritional assessment in adults with self-reported non-coeliac gluten sensitivity

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Oslo, September 2016

Kjersti L Rolfsen

Abstract

Background: The mechanisms behind non-coeliac gluten sensitivity (NCGS) are not fully understood although clinical symptoms have shown to subside after gluten withdrawal. Self-administration of a gluten-free diet (GFD) without medical supervision is common for NCGS patients, resulting in dietary restrictions that can cause macro- and micronutrient deficiencies.

Objectives: The objective of this thesis was to describe nutritional status, clinical symptoms and health-related quality of life (HRQoL) in adults with self-reported NCGS on a GFD.

Methods: Baseline characteristics were collected from 66 NCGS patients participating in the study 'Gluten challenge in patients with non-coeliac gluten sensitivity' at Oslo University Hospital (OUH) Rikshospitalet. Nutritional status was evaluated through anthropometrics, laboratory data and diet history. Intake of nutrients was estimated by a 7-day food diary. Symptoms were reported via completion of four symptom specific questionnaires assessing gastrointestinal symptoms, fatigue, depression and subjective health complaints. HRQoL was reported by Short-form 36 (SF-36). The term nutritional assessment encompasses all these factors, and is therefore the overarching method used in this study.

Results: Results from nutritional assessment in NCGS patients showed that the average body mass index (BMI) was within upper-normal range (24.8 kg/m²). Nutrient deficiencies were hardly seen. Analysis of the food diaries showed that NCGS patients had a higher total fat intake (43 E %), too high intake of saturated fat (14 E %) together with a lower carbohydrate intake than recommended (39 E %), and a low intake of dietary fibre (19 g). Intakes of micronutrients were lower than recommended for calcium, iodine, iron (females), D vitamin and folic acid. Overall, the NCGS patients had persistent symptoms on a GFD. Extra-intestinal symptoms, in particular fatigue and mild depression, were most arduous. HRQoL was reduced for some aspects, especially for the scale comprising fatigue and loss of energy termed vitality.

Conclusion: NCGS patients were found to have good nutritional status regarding BMI and laboratory values. Their high proportion of energy from fat and the sub-optimal intakes of iodine, calcium, iron, D vitamin and folic acid, may put patients at risk of nutrient deficiencies. This highlights the importance of dietary education and nutritional follow up. The reduced diet quality may be linked to unnecessary dietary restrictions. Despite being on a GFD, extra-intestinal and gastrointestinal symptoms were present. Though, patients seemed to perceive their health to be better after adapting to a GFD.

List of abbreviations

Anti-DGP	Anti-deaminated gliadin-peptide
Anti-EMA	Anti-endomysium
Anti-tTG	Anti-tissue transglutaminase
Anti-AGA	Anti-gliadin antibodies
ATIs	Amylase-trypsin inhibitors
BDI-II	Beck Depression Inventory-II
BMR	Body mass index
CD	Coeliac disease
CRF	Clinical report form
DBPC	Double-blind placebo controlled
EI	Energy intake
EGD	Esophagogastroduodenoscopy
FODMAP	Fermentable oligo, di-, monosaccharides and polyols
GBB	Giessen Subjective Complaint List
GFD	Gluten-free diet
GSRS-IBS	Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
IBS	Irritable bowel syndrome
IELs	Intraepithelial lymphocytes
IFN- γ	Interferon-gamma
Ig	Immunoglobulin
LCD	Low carbohydrate diet
NCF	Norwegian Coeliac Society
NCGS	Non-coeliac gluten sensitivity
NCP	Nutrition care process
NHANES	National health and nutritional examination survey
OUH	Oslo University Hospital
REK	Regional Committee for Medical Research Ethics
SF-36	Short Form-36
SHC	Subjective Health Complaints
VAS	Visual analogue scale
WHO	World Health Organisation

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1 Introduction

1.1 Background

1.1.1 Gluten

Gluten is the storage protein found as gliadin and glutenin in wheat. Similar proteins are also found in rye (hordein), barley (secalin) and in other related grains. The major seed-proteins have high content of the amino acids glutamine and proline. They are called prolamines, and dissolve only in alcohol (1). Gluten is well-known for its viscoelastic properties in breads and pastas (2). Gluten is poorly digested in both healthy individuals and in patients with coeliac disease (CD). However, unlike in the case of healthy individuals, the gluten peptides in CD patients cause intestinal inflammation (1).

Wheat has been a food crop for the past 10 000 years (3). In terms of human evolution, this is considered to be too short a time for developing a coping strategy towards gluten, causing the two best-known adaptive immune responses, CD and wheat allergy (4, 5). After the First World War, cultivation of wheat became more efficient, and the need for more-resistant varieties led to changes in the protein content and the immunogenic properties of wheat (6, 7). Further, to shorten the baking process concentration of gluten in bakery products has increased in addition to being widely used in the food industry of other products (4). The increased exposure to the modernized wheat art, together with the development of improved diagnostic tools for identifying conditions linked to gluten exposure, may be involved in the increased prevalence of gluten-related disorders (8-10).

1.1.2 Coeliac disease

CD is a well-studied chronic autoimmune-mediated enteropathy. It is triggered when genetically disposed individuals carrying the human leukocyte antigen (HLA) -DQ2 or -DQ8 consume gluten (11). Worldwide, CD has a prevalence of approximately 1 %, and appears to be on the increase (12). CD is distinct from wheat allergy, which is an Ig E-mediated reaction to the proteins in wheat (10).

In CD patients, the subsequent inflammation within the small intestine following gluten exposure results in destruction of the intestine and gradual cessation of intestinal functions,

ultimately degrading nutrient absorption (13). Malabsorption of fat-soluble vitamins (e.g. vitamin D), iron, B₁₂, folic acid, calcium and zinc is common in untreated CD patients (14). This can in turn lead to development of bone disease, iron deficiency anaemia, neurological disorders and other haematological manifestations (15). Earlier, CD was viewed as a malabsorption disorder with diarrhoea and weight loss, symptoms less frequently seen today. Overweight and obesity are currently not uncommon in CD (16). The severity of intestinal changes varies, and the symptoms of coeliac disease may seem diffuse (1, 17). Common gastrointestinal symptoms are weight loss, diarrhoea, flatulence, bloating and stomach pain. Extra-intestinal symptoms include joint pain, fatigue, bone diseases and skin disorders (1, 17, 18). There is also an increased risk for other auto-immune diseases (15).

Treatment of CD involves strict adherence to a gluten-free diet (GFD), which in most cases will result in healing of the small intestine and improved general health (17). Diagnosis of CD is made through duodenal biopsies and serological testing in patients who consume gluten. Duodenal biopsies are evaluated according to the Marsh gradation. Marsh grades 1 to 3 are compatible with CD, and includes signs of villous atrophy, crypt hyperplasia and inflammatory cells including intraepithelial lymphocytes (IELs: $\geq 25/100$ enterocytes) (19). Serological testing for CD mainly involves detection of the antibodies immunoglobulin A (anti-IgA) to tissue-transglutaminase 2 (anti-TG2) and immunoglobulin G (IgG) to deaminated gliadin peptide (anti-DGP) (17).

1.1.3 Coeliac disease and non-coeliac gluten sensitivity

The prevalence of CD does not seem to correspond to the number of people adhering to gluten-free diets, nor the gluten-free market which has expanded greatly in recent years (20). This expansion in GFD could in part stem from media focus presenting gluten as something toxic, in addition to the publicity given to celebrities who follow GFD for a healthier lifestyle or as a means to lose weight (21). Some of those who adopt a gluten-free lifestyle do so to obtain relief from symptoms or various conditions, often without medical support for their dietetic change. These individuals may belong to the NCGS entity, as they show no signs of CD or wheat allergy. NCGS is described as an intermediary condition between the CD spectrum and conditions with symptoms like those of irritable bowel syndrome (IBS), as all these conditions have overlapping symptoms (22, 23). NCGS falls between CD and IBS due to uncertainties whether it is gluten, carbohydrates or other components in wheat that generate symptoms (23-26). As a substantial proportion of NCGS patients are showing HLA

haplotypes and seronegative Marsh 1 lesions, NCGS is suggested to belong to the spectrum of CD, so called coeliac-light (27). In any case, there does exist scientific backing for gluten-induced symptoms in non-coeliac patients (24, 28-32). In 1978–80, a description of NCGS as a unique entity showed relief in symptoms when gluten was avoided, and relapse of symptoms after gluten re-introduction (33, 34). In the past decade, the entity has been rediscovered. After Sapone et al. (35) published a paper on the clinical and pathophysiological features of NCGS in 2010, more than 2000 publications about NCGS have been written, confirming the widespread lack of knowledge about NCGS (36). Further investigation of NCGS is needed to get a better understanding of the similarities and differences between NCGS, other gluten-related conditions and IBS.

Self-assessed NCGS is a worrisome trend. Cases of CD may be present, and with adherence to a strict GFD to avoid adverse outcomes, extensive and unnecessary food avoidances without proper instruction can cause nutrient imbalances and deficiencies. Whether malabsorption is common in NCGS is unknown. In view of the heterogeneity and diversity of NCGS patients, better knowledge about nutritional status is needed: such patients may be without general dietary advice.

1.2 Non-coeliac gluten sensitivity

1.2.1 Pathogenesis

The pathogenesis of NCGS is not fully understood, and no biomarker is detected. Studies have noted the dominant action of the innate immune system through expression of Toll-like receptor 2 (TLR2) (37), but the adaptive immune system can also be involved, as increased levels of interferon gamma (IFN- γ) in small intestine biopsies have been found (38). According to the latter findings, IgG to anti-gliadin antibodies (anti-AGA) were detected in 50 % of NCGS patients, providing further evidence that the adaptive immune system plays a role in the development of NCGS (39, 40). Discordant data exist as to whether NCGS patients display reduced intestinal barrier function caused by gluten (37, 41). Interesting new research has found increased epithelial cell damage and intestinal barrier defects in NCGS patients that caused translocation of microbial products into the circulation and activation of an acute systemic immune response after ingestion of wheat and related grains. This reaction to wheat diverged from what was found in CD patients and was absent in healthy controls, giving

possibilities to find objective markers of NCGS (42). There is also a possibility that gluten can directly cause gastrointestinal symptoms by increasing smooth muscle contractility and raising luminal water content in the intestine, as is seen in HLA-DQ8 transgenic mice (43).

A novel aspect of the pathogenesis of NCGS is that non-gluten proteins in wheat, amylase trypsin inhibitors (ATIs) and lectins, are shown to be prominent activators of the innate immune system. Lectins can impair intestinal permeability (26). They both may contribute to the development of CD, IBS and perhaps play a role in NCGS (44).

1.2.2 Epidemiologic and clinical picture

The prevalence of NCGS has not yet been established, but analysis of population-based data from the USA – the 2009/2010 National Health and Nutrition Examination Survey (NHANES) – showed that 0.6 % of those surveyed followed a GFD without having CD (45), although this study was not specifically designed to detect NCGS patients. An expected higher prevalence of 6 % has been found in a CD-specialized centre (5). Further, in a large cohort from various referral centres for gluten-related disorders in Italy there was a NCGS/CD prevalence ratio of 1.15:1, suggesting that the prevalence of NCGS is slightly higher than for CD (~1 %) (12, 46). NCGS is also seen in children, with prevalence less than 3 % in Italian paediatric centres for gluten-related disorders (46). Data from New Zealand have shown that as many as 5 % of the children living there avoid gluten, mainly because of non-specific abdominal pain (47). NCGS can be detected at any age, but the syndrome appears to occur more frequently in female adults, with an average age of about 40 years and a female/male ratio of 5:1 (46).

As NCGS patients experience a wide range of symptoms, it has been suggested to be a syndrome rather than a distinct disease (48). Symptoms induced by gluten are usually experienced soon after gluten ingestion (hours to few days), disappearing or improving after gluten withdrawal, and recurring upon gluten challenge (5, 39). Most patients complain of two or more symptoms (39). Lower gastrointestinal symptoms reported by NCGS patients (Table 1) include bloating, abdominal pain/discomfort, diarrhoea, altered bowel habits and constipation (46). These symptoms are overlapping with those reported in IBS patients (49, 50). Less common gastrointestinal symptoms identified in NCGS are epigastric pain, nausea, aerophagia, gastroesophageal reflux disease and aphthous stomatitis (46). The most frequent extra-intestinal manifestations in NCGS are reduced well-being and fatigue (46). Other extra-

intestinal features of NCGS are neurological symptoms including headaches, foggy mind, limb numbness, and joint/muscle pain and psychiatric manifestations including depression and anxiety (46). Regarding psychiatric conditions, an association has been proposed between NCGS and autism spectrum disorders (51, 52), attention deficit hyperactivity disorder (ADHD) (53, 54) and schizophrenia (55, 56), with discordant results as to the beneficial effects of a GFD (57). In children with NCGS, abdominal pain and diarrhoea are the most common symptoms (58).

Studies have found additional responses to foods in NCGS patients, mainly lactose intolerance and Ig E mediated allergy to food or inhalants (46). Small intestinal bacterial overgrowth are also found in NCGS patients (59).

In summary, NCGS patients are a heterogeneous group with various aspects of the aforementioned phenotype presented. Studies exploring NCGS have used various inclusion and exclusion criteria and a range of different methods to investigate relevant outcomes, with discordant results in the characterization of this new phenomenon.

Table 1. Clinical manifestations in NCGS.

Gastrointestinal	Extra-intestinal	
<i>Very common:</i>		
Bloating	Lack of wellbeing	
Abdominal pain	Tiredness	
<i>Common:</i>		
Diarrhoea	Headache	
Nausea	Anxiety	
Aerophagia	Foggy mind	
Gastroesophageal reflux	Numbness	
Aphthous stomatitis	Join or muscle pain	
Alternating bowel habits	Skin rash or dermatitis	
Constipation		
<i>Undetermined:</i>		
Haematochezia	Weight loss	Ingrown hairs
Anal fissures	Anaemia	Oligi- or polymenorrhea
	Loss of balance	Sensory symptoms
	Depression	Disturbed sleep pattern
	Rhinitis/asthma	Hallucinations
	Weight increase	Mood changes
	Intestinal cystitis	Autism
		Schizophrenia

Abbreviations: NCGS, non-coeliac gluten sensitivity. Reproduced from Catassi et al. (8).

1.2.3 Overlap with Irritable Bowel Syndrome

IBS is a functional bowel disorder characterized by abdominal discomfort or pain and altering bowel habits (50). A diagnosis of IBS is set after controlling for symptoms according to Rome III criteria for IBS: The symptoms must be present ≥ 6 months and their presence ≥ 3 days a month the last 3 months. Additionally, two of the following situations need to be present: 1. relief in symptoms after defecation, 2. experienced change in stool frequency at symptom debut, 3. change in stool consistence at symptom debut (60). The prevalence of IBS among adolescents and adults is 10-20 % worldwide, with female predominance. The symptoms experienced by IBS patients impair quality of life and results in high healthcare costs (50). The connection between IBS, NCGS and CD is illustrated in Figure 1.

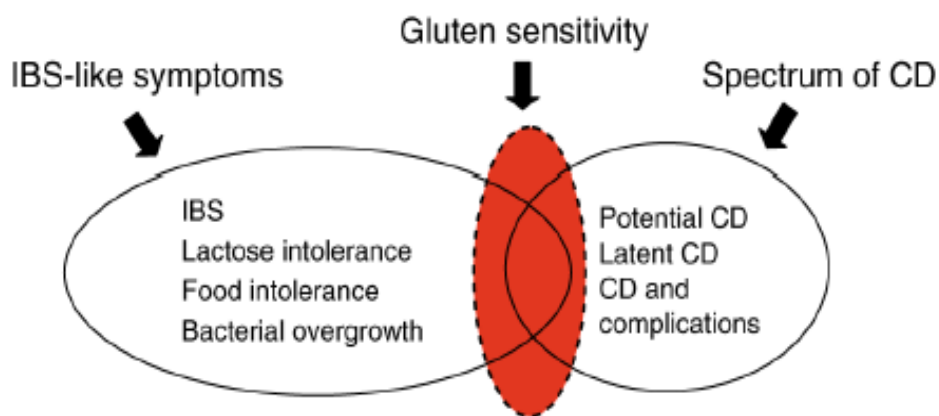


Figure 1. Non-coeliac gluten sensitivity (NCGS) may be one of the underlying mechanisms in IBS and may not necessarily belong to the spectrum of coeliac disease (CD). Reproduced from Verdu et al. (23).

Considering the relationship between IBS and CD, a meta-analysis found that 4 % of IBS were having CD (61), and a considerable proportion of treated CD patients still experience IBS-like symptoms (11), may be due to non-adherence (62). As such overlap exist, screening for CD in diarrhoea-predominant IBS and IBS with mixed bowel habits has been recommended (63).

Like NCGS, the underlying pathological mechanisms behind symptoms generation in IBS is poorly understood (23). NCGS can be considered as a sub-type of IBS as the clinical picture includes IBS-like symptoms (46). Further, the presence of symptoms fulfilling the criteria for IBS is frequently described in suspected NCGS populations (24, 46, 64). Though, it is

suggested that the symptoms in NCGS are more constant over time compared to more fluctuating symptoms in IBS, often related to a specific meal (65). A main difference is that NCGS patients report relief in symptoms after gluten withdrawal while a diet low in fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) alleviates symptoms in most of IBS patients (66). However, when gluten is eliminated from the diet in NCGS patients, the intake of fructans (a high FODMAP carbohydrate) is also reduced (67), and controversies exist whether it is gluten or osmotically short chain carbohydrates that cause symptoms in NCGS (24, 25).

Biesiekierski et al. (68) found that about one fifth of NCGS patients reported symptoms despite being gluten-free, and many avoided FODMAPs in addition to gluten for further symptom control. Especially the FODMAP disaccharide lactose is found to be excluded in large proportion of NCGS patients (46, 59). Still, there is little evidence for widespread avoidance of other FODMAP containing foods than grains in NCGS patients, reducing the possibility for a main role of FODMAPs (7). On the other hand, beneficial effects of gluten have been shown in patients with diarrhoea-predominant IBS, which suggests that at least a proportion of patients with IBS can improve on a GFD suiting the NCGS diagnosis (29).

Food intolerances are thought to be widespread among IBS patients where dietary restrictions are common, but there is controversy as to whether intolerances are a common pathogenic feature in IBS (69, 70). Food intolerances have also been found in NCGS patients fulfilling criteria for IBS (46, 71). In such cases, dietary restrictions could cause macro- and micronutrient deficiencies, and dietary approaches should be implemented with caution (70, 72-74).

Somatic complaints without physiological explanations are referred to as somatization. They might play a role in both NCGS and IBS (75), as there is a strong bidirectional connection between the brain and the gut (76-78). Main components within somatization are psychological and psychosomatic factors, as well as personality traits (75). It has been suggested that symptoms in IBS patients are highly related to the level of somatization (77). However, Brottveit et al. (75) found no tendency to somatization in NCGS patients or CD patients.

Further research is needed to investigate if NCGS and IBS coexist or if NCGS is a sub-type of IBS.

1.2.4 Diagnostic criteria

Patients fulfilling diagnosis of NCGS report both gastrointestinal and extra-intestinal symptoms when exposed to gluten and relief from these symptoms when gluten-containing foods are eliminated from their diet. Further, CD and wheat allergy must have been ruled out (7). CD is excluded when normal levels of IgA TG2, IgA endomysial (EmA) and IgG to deaminated gliadin peptide (DGP) are seen together with the absence of villous atrophy in intestine biopsies (9). Wheat allergy is discarded if serum IgE antibodies to gluten are normal, in addition to a normal skin-prick test for wheat allergy (10). All these tests must be conducted while the suspected NCGS patient still consumes gluten.

In clinical practice, patients are often found to have started to follow a GFD already, due to self-diagnosed NCGS. In such situations, gluten-provocation for two weeks is recommended (11, 79). After the exclusion of other gluten-related conditions, confirmation of the diagnosis is best settled by a double-blind randomized placebo controlled (DBPC) gluten challenge, but this is resource-intensive and has not yet been incorporated into regular clinical practice (8).

In Norway diagnosis of NCGS is made after an open gluten challenge of three days with supplementary self-assessed symptoms questionnaires, answered prior to the gluten challenge and after. Change in symptom load is then evaluated by a gastroenterologist and a dietitian. An NCGS diagnosis will entitle the patient to reimbursement from the Norwegian Labour and Welfare Administration, in order to finance a gluten-free diet. A standardized procedure for diagnosing NCGS is lacking in the country's primary care system, creating a burden on the specialized centres. Whether NCGS is a permanent or a transient condition has yet to be established. As a result gluten-reintroduction should be done after 1-2 years (39, 80).

About 50 % of NCGS patients have the HLA-DQ2 or HLA-DQ8 haplotypes (24, 39, 71, 81) – less than in CD patients, but higher than in the general population (11, 82). These differences may mean that the HLA variants have a role in NCGS pathogenesis, but this is disputed (42, 83, 84). Unlike CD, the mucosa of the intestine remains undamaged in NCGS patients. Despite this, IEL infiltration is found in a considerable proportion of patients, indicating an ongoing low grade inflammation (37-39, 46). The IEL infiltration in NCGS patients is higher than in healthy individuals but lower than that found in CD patients, and appears to be unchanged after gluten exposure (38). IgG AGA is found in approximately half of NCGS patients. That could possibly be a marker of the beneficial effect of gluten withdrawal, as these antibodies have been shown to disappear after six months on a GFD,

with levels rising again after gluten exposure. In contrast, about half of CD patients had persistent IgG AGA after commencing a GFD (40).

Table 2. NCGS diagnostic criteria, distinguished from CD.

Diagnostic tools	Coeliac disease	Non-coeliac gluten sensitivity
Coeliac disease serology:		
Anti-tissue transglutaminase	Positive	Negative
Anti-gliadins antibodies	Positive	Positive (50 % of cases)
Anti-endomysial antibodies	Positive	Negative
Deaminated gliadin peptide antibodies	Positive	Negative (Marsh 0–1)
Duodenal histology (Marsh-Oberhuber classification)	Positive (Marsh 1–3)	Absent/present
HLA haplotypes (DQ2-DQ8)	Present	Negative
IgE-based assays (prick tests or serum IgE dosage)	Negative	Negative
Clinical features	Troubles caused by gluten ingestion and their disappearance on gluten-free diet	Troubles caused by wheat ingestion and their disappearance on gluten-free/wheat free diet

Abbreviations: NCGS, non-coeliac gluten sensitivity; CD, coeliac disease; HLA: human leukocyte antigen, Ig: immunoglobulins. Reproduced from Mansueto et al. (85).

1.2.5 Nutritional status

An optimal nutritional status is defined as a condition of sufficient energy and nutrient intake to maintain a healthy body composition and function (86). Adequate intake promotes growth, development, maintaining health, helps to protect the body from illness and diseases and supports physical activity. An insufficient dietary intake over time will result in wasting of body tissue, consequently leading to weight loss. Children and older people are in particular vulnerable in this respect. Dietary inadequacy or imbalance can also be found in normal- or overweight individuals reducing nutrition wellness.

Gluten-free diet

Wheat and wheat-derived products are the main components in the human diet worldwide today (87). According to a Norwegian national nutrition survey (Norkost 3) conducted between 2010 and 2011, breads and cereal products provided 27 % of the energy intake in

adult females and males. Further, bread was found to be the main source of carbohydrates, fibre, iron, folic acid, thiamine and magnesium, and the second main source of protein in the Norwegian diet (88). Hence, excluding cereals increases risk of inadequate intake of these nutrients, unless they are replaced by nutritious gluten-free cereals and pseudocereals (like gluten-free oats, quinoa, buckwheat and amaranth) in adequate amounts (89).

Most patients with suspected NCGS are on a self-administered GFD. They seem to adhere well to the diet, in line with coeliac patients (90). GFDs have been shown to be higher in fat and lower in fibre compared to a normal diet (91), and nutrient inadequacies in coeliac patients on GFD have been found (14, 92). Nutritional status at diagnosis and after treatment with GFD has not been well described in NCGS patients. Volta et al. (46) found weight loss to be present in 25 % of NCGS patients and Carroccio et al. (71) found that weight loss was less frequent in suspected NCGS patients (35 %) compared to CD patients (52 %). This was also seen for anaemia, found in 24 % and 78 % of NCGS and CD patients, respectively (71). In another study, the same authors found that 47 % of the NCGS patients had osteopenia or osteoporosis, a lower prevalence as compared to CD patients (64 %). This was associated with low body mass index (BMI) and insufficient intake of calcium, specifically affecting those with other food intolerances (93). Inadequate vitamin D status could also be a part of this clinical picture (94). Low levels of ferritin, vitamin D and folic acid have been found in NCGS patients, but less frequent than in CD patients (14, 46). Low-grade inflammation in the intestine may cause malabsorption, but whether this is widespread among NCGS patients remains undetermined (48). Moreover, nutritional deficiencies do not appear typical of the NCGS diagnoses, though awareness and guidelines for follow-up are needed.

1.3 Nutritional assessment

Nutritional assessment is the first step in the Nutrition Care Process (NCP), a method that facilitates the dietitian's practice through a systematic work process that offers optimal care to the service users, illustrated in Figure 2. Nutritional assessment involves identification of nutritional needs and the causes underlying nutrition-related health issues. The goal of nutrition assessment is to gain adequate information to make skilled judgement about nutritional status. The screening process for identifying nutrition-related problems includes assessment of anthropometrics, laboratory data, dietary history, medical history and current symptoms together with environmental/behavioural/social status (95).

In self-reported NCGS, first of all, the need for a GFD has to be settled. If such is stated, evaluation on how this diet is implemented is important to reduce risk of malnutrition and adverse health outcomes. In the majority of self-reported NCGS, the GFD is implemented without dietary advice from health professionals which increases likelihood for nutritional inadequacies (68, 96). Hence, nutritional assessment in self-reported NCGS is warranted. A suitable nutritional assessment for NCGS patients should include anthropometry, laboratory data of nutritional biomarkers, dietary intake, GFD adherence, as well as reported clinical symptoms and health-related quality of life (HRQoL).

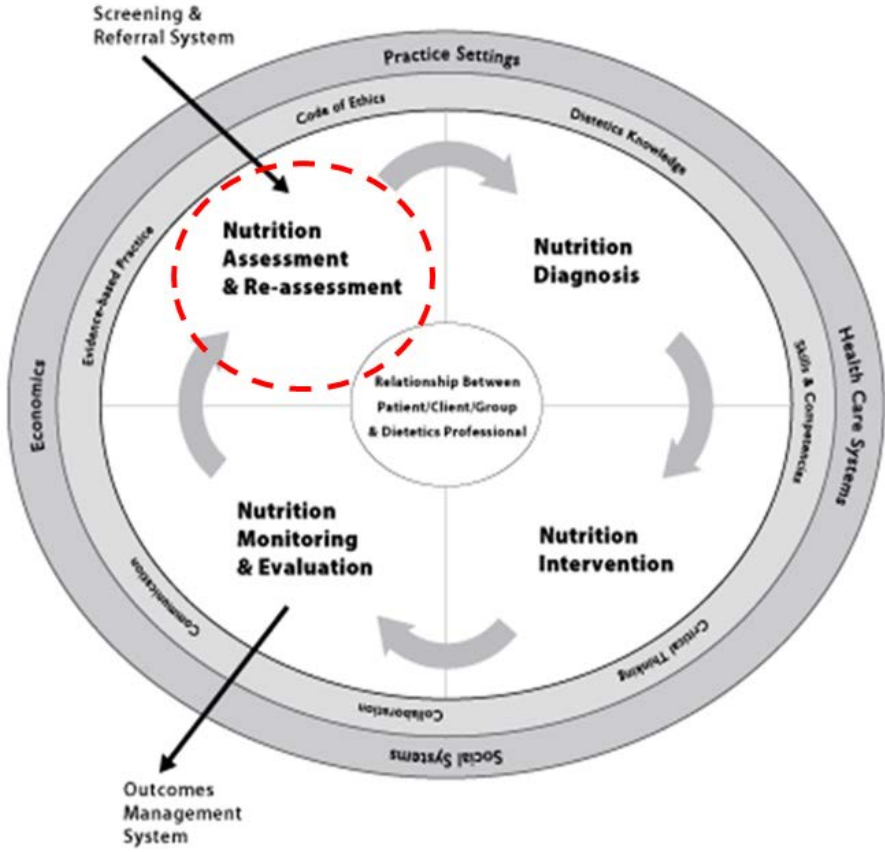


Figure 2. Nutrition Care Processes (NCP) for nutrition and dietetic practice (95).

1.4 Clinical symptoms

Little research has been conducted on investigating symptoms in NCGS on a GFD. In a recent Norwegian study by Brottveit et al. (75), somatization, personality traits, anxiety and depression, and HRQoL in NCGS patients were measured and compared to CD patients and healthy controls. The results showed that NCGS patients did not exhibit somatization tendencies; personality traits were normal, and anxiety and depression were not present. Further, HRQoL was reduced for some aspects only. All these parameters were comparable to CD. However, after a short gluten challenge, NCGS patients reported more gastrointestinal symptoms than did CD patients (75).

1.4.1 Gastrointestinal symptoms

NCGS is generally characterized by patients reporting relief in gastrointestinal symptoms when gluten is avoided in the diet, but symptoms seem to persist in some patients (59, 68). Few researchers have looked into the mechanisms behind the gastrointestinal symptoms experienced by NCGS patients. Foods can trigger symptoms from the gut through various mechanisms, including immune and mast cell activation (food proteins, e.g. gluten), mechano-receptor activation via luminal distension (FODMAPs (gluten)) and chemosensory activation (e.g. salicylates) (43, 97).

1.4.2 Fatigue

Fatigue is a state characterized by severe tiredness that cannot be explained by a specific disease or psychiatric disorder and which reduces daily functioning capacity (98). Fatigue is a non-specific subjective symptom that is difficult to define and measure. The underlying causes are multifactorial, and include physical exhaustion, mental exhaustion and nutritional deficiencies (iron deficiency and anaemia) (98-102). In addition, recent science indicates that dysbiosis in the microbiome of the colon may cause fatigue (103). In NCGS, fatigue is the most bothersome extra-intestinal symptom reported, where the underlying causes are unknown (46).

1.4.3 Mental health

As defined by the World's Health Organization (WHO), mental health refers to the level of perceived psychological well-being, and affects mood and behaviour. Mental disorders may develop in interaction between psychological, social and biological factors (104). Both anxiety and depression lie within the definition of mental disorders. Anxiety and depression have been described in NCGS patients (46). Peters et al. (105) recently found a possibility for gluten-induced depression after three days with gluten challenge, and held that this could be the reason why these patients felt better on a GFD.

1.4.4 Health-related quality of life

HRQoL is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. It is distinguished from the individual's general perceived quality of life by referring solely to the impact of health status on quality of life (106). Little research has been conducted on HRQoL in NCGS patients. Brottveit et al. (75) found that HRQoL was reduced for physical functioning, general health, bodily pain and social functioning, compared to healthy controls. Further studies should address HRQoL in NCGS patients.

2 Objectives

The objective of this thesis was to contribute to our knowledge about nutritional status and diet as well as symptoms and HRQoL in patients with self-reported NCGS. The main aim was to perform nutritional assessment, consistent with the Nutrition Care Process (NCP). The specific aims of this thesis were as follows, regarding NCGS in particular:

- to evaluate BMI through anthropometric measurements
- to describe nutrient intake of macro- and micronutrients
- to describe micronutrients status by relevant blood biomarkers
- to evaluate adherence to the gluten-free diet
- to evaluate clinical symptoms and HRQoL

3 Subjects and methods

3.1 Study design

This thesis is a part of a randomized double-blind placebo-controlled trial investigating nutritional status and clinical symptoms in suspected NCGS patients after exposure to gluten, FODMAPs and placebo. Data analysed in this thesis have been collected from the baseline of this clinical trial, a period of seven days. Hence, this study is based on a cross-sectional study. During baseline, nutritional status was determined using anthropometric measures and blood samples, intake of nutrients was evaluated by a 7-day food diary and adherence to the gluten-free diet and symptom load were measured by self-administered questionnaires. All parameters should reflect the patients normal situation on a GFD. Recruitment and data collection were conducted in the period October 2014 to January 2016. The study is a collaborative project between the Department of Gastroenterology at Oslo University Hospital (OUH) Rikshospitalet and the University of Oslo Centre for Immune Regulation.

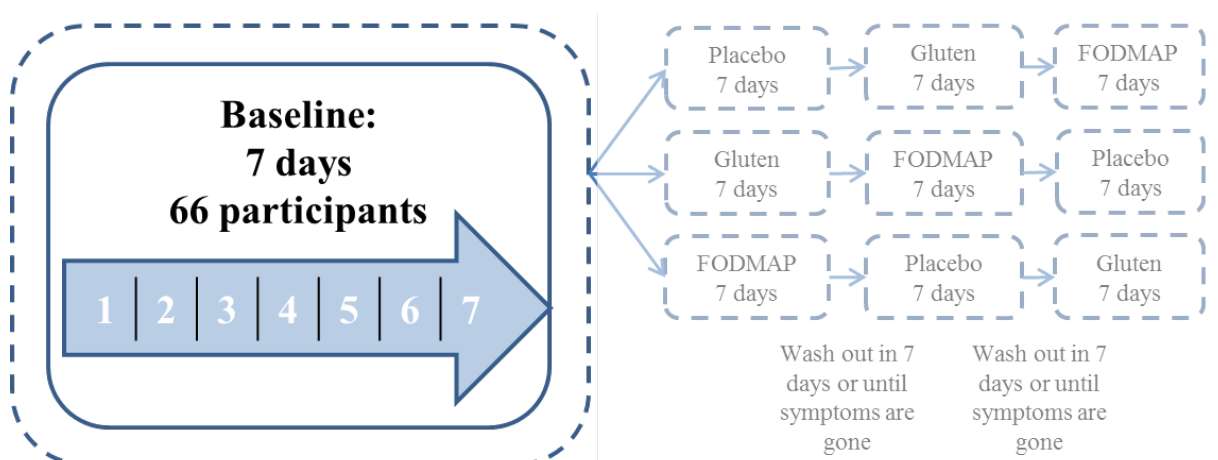


Figure 3. Study conduct of the main study ‘Gluten challenge in patients with self-reported non-coeliac gluten sensitivity’.

Ethics

The main study ‘Gluten challenge in patients with non-coeliac gluten sensitivity’ was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2013/1237) and the local Privacy Commissioner for Research at OUH. Written informed consent was obtained from the participants (Appendix 1).

Pilot testing

A pilot test was performed with two participants, to check the feasibility of all measures involved in the study. One of participants was excluded due to sesame seed allergy. Data from the pilot participants do not form part of the study results.

3.2 Subjects and recruitment

The target population in the main study was adult patients with suspected NCGS living in the vicinity of Oslo. Patients should not have had prior investigation for NCGS by challenge, and they were to report relief of symptoms on GFD. CD was required to have been disproved by negative biopsy of the duodenal intestine or by negative test for human leukocyte antigen, HLA-DQ2/HLA-DQ8, and wheat allergy by negative wheat specific IgE while on a gluten containing diet. Study patients were recruited by the Gastroenterology Division at OUH and by announcements in social media and through the Norwegian Coeliac Society (NCF). Recruiting from other hospitals in Norway's South-East Health Region was also acceptable. Invitation letter are shown in Appendix 2.

Inclusion criteria:

- aged 18-80 years
- coeliac disease excluded by negative biopsy and/or negative genotyping
- compliance with GFD for > 6 month
- symptoms controlled on GFD

Exclusion criteria:

- pregnant or breastfeeding
- serious reactions after ingestion of minor amounts of gluten
- chronic, active gastrointestinal disease
- usage of immunosuppressive drugs the past 3 months
- ongoing infection

3.3 Study conduct

An overview of the study conduct and how data was collected is depicted in Figure 4.

Before the first visit at OUH Rikshospitalet, participants received the symptom-specific questionnaires by post, in addition to written information and a consent form. They were asked to answer the questionnaires before the first consultation at baseline. The symptom-specific questionnaires would reflect the last seven days of the patients` normal situation in terms of gastrointestinal symptoms, fatigue, depression, general health complaints and HRQoL.

Baseline visit was performed by a dietician or a master student using a Clinical Report Form (CRF), see Appendix 3. Completed questionnaires were collected and checked. Additionally, each patient completed a self-administered adherence questionnaire, and a knowledge test.

Participants received instructions on how to record the food diary and the 7-day visual analogue scale (VAS) dairy for gastrointestinal symptoms. Baseline registrations were returned on the second visit.

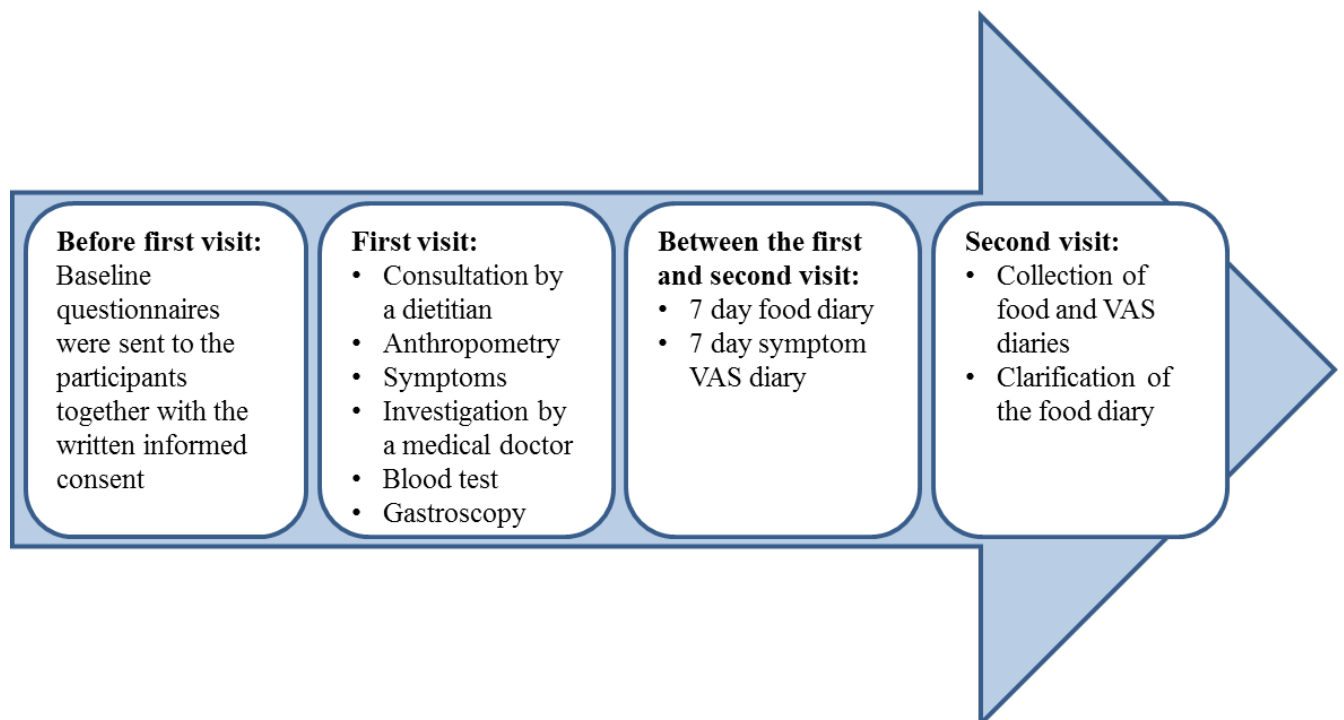


Figure 4. Conduct of baseline, duration: seven days

3.4 General characteristics

3.4.1 Patient characteristics

General information about age, work situation, activity level, smoking status, dietary habits and medical characteristics were collected via a structured interview (CRF) during the baseline consultation. Information about dietary habits were obtained from questioning about other food avoidances apart from gluten in addition to alcohol consumption. The food diaries gave information about supplement use among patients.

3.4.2 Medical characteristics

A medical doctor measured the blood pressure and heart rate of each patient. In addition a physical examination was performed (cardiac/pulmonary/abdomen). Patients were also asked if they had any current disease in addition to their gluten sensitivity and information about family history of coeliac disease was obtained. To check if symptom burden was related to IBS, questions according to the Rome III criteria for IBS were asked.

Biopsy, histological evaluation and coeliac serology

Gastroscopy was performed before or after the day of the first consultation, and outside the period of diet and symptom registration. Small bowel biopsies were collected by performing an esophagogastroduodenoscopy (EGD), GIF-HQ190 scope with disposable forceps (from Olympus, Hamburg, Germany) before start of the gluten challenge. Patients were offered local anaesthesia with xylocaine spray and /or conscious sedation using midazolam intravenously. We collected ten biopsies from each patient: six were formalin-fixed and paraffin-embedded for morphological examination, and four were stored in RNA later (Qiagen Nordic, Oslo, Norway). Histological evaluation was performed routinely by an experienced pathologist, using the revised Marsh criteria (107-109). Marsh type 0 refers to normal mucosa, type 1: infiltrative with increased amounts of intraepithelial lymphocytes (>25/ 100 enterocytes); type 2: hyperplastic; types 3a, 3b, and 3c: increasing degree of destructive lesions. Participants showing Marsh >1 were not included in the study.

Coeliac disease serology included serum antibody titres of anti IgA-TG2 and anti IgG-DGP. In addition, genotyping of HLA-DQ2 and HLA-DQ8 were performed. Analyses were performed at the Department of Medical Biochemistry at OUH Rikshospitalet.

3.5 Nutritional status

3.5.1 Anthropometry

Body weight and height were measured at the first baseline visit. Body weight (kg) was measured by Seca 772021® electronic scale (Vogel & Halke GMBH & Co). Height measurement (in cm) was performed by a Seca 242® fixed electronic measuring rod (Vogel & Halke GMBH & Co). Height and weight were measured with the participant fully dressed but lightly clad, without outer clothing or footwear. BMI was calculated as weight (kg) divided by height² (m²) (kg/m²).

3.5.2 Nutritional biomarkers

At the baseline visit, non-fasting blood tests were taken to investigate biomarkers of nutritional status. Blood samples were collected for analysis of, iron, transferrin, ferritin, haemoglobin (Hb), calcium, vitamin B₁₂, folic acid (B9), vitamin D, haemoglobin A1c % (HbA1c), free-thyroxin (FT4), thyroid-stimulating hormone (TSH) and parathyroid hormone (PTH). Analyses were performed at the Department of Medical Biochemistry at OUH Rikshospitalet; analyses of vitamin D metabolites were performed at the Hormone Laboratory, OUH Aker. Reference values were those utilized at OUH Rikshospitalet (Laboratory manual for OUH Rikshospitalet and Radiumhospitalet). Vitamin D status was evaluated against the reference values recommended by NNR12 regarding deficiency (< 25 nmol/L) and a suboptimal intake (50 nmol/L) (110).

3.5.3 Food diary

A 7-day food diary gave information about intake of macro- and micronutrients. The patients' diet in the baseline period was to demonstrate their usual intake on a GFD. The diet was not encouraged specifically to be FODMAP-free.

In order to estimate nutrient intake, participants were asked to keep an extensive food diary for seven consecutive days (see Appendix 4). Participants were given instructions, checklists, and examples to guide them in making their food diaries. Amounts were recorded in household measures, weight or by a picture book with known portion sizes. All participants were thoroughly instructed in the method at the first study visit. The name of the food or dish was registered, together with the amount consumed, how it had been prepared and the time of intake. Participants were also asked to register recipes of the homemade dishes they consumed. The food diary gave room for describing snacks and desserts in addition to main dishes.

The Diet Planner

Data from the food diaries were analysed using the *Diet Planner* (111), a web-based food diary that calculates nutrient intake. The Diet Planner was developed by the Norwegian Food Safety Authority and the Norwegian Directorate of Health in 2014. Food items and food courses listed in the *Diet Planner* are based on the Norwegian Food Composition Table, Weights and measures for foods and Recommendations for Diet, Nutrition and Physical Activity (112-114). After the latest update in 2015, the *Diet Planner* contains 1543 food items and data on 38 nutrients.

Calculating nutrient intake

Food diaries were registered into weekly menus in the *Diet Planner*. The gluten-free products of several gluten-free brands were not available in the *Diet Planner* and micronutrient content in gluten-free products was lacking from both packaging and brand web pages. The firms Wasa, Semper, Finax, Fria, Det Glutenfrie Verksted, Schär and Hatting were contacted for product-sheets for their gluten-free products. None of the producers had data on micronutrient content in their gluten-free products, so comparable gluten-free products already in the *Diet Planner* were used as a replacement for gluten-free products from the different manufacturers.

When a common naturally gluten-free dish was noted, rather than the specific contents of the dish, the recipe available for this dish in the *Diet Planner* was used. In some cases, participants noted eating a gluten-free dish where there was no corresponding gluten-free recipe in the *Diet Planner*. In these cases, the non-gluten-free variant of the dish available in the *Diet Planner* was used. Occasionally participants reported consuming a gluten-free dish for where neither a gluten-free nor a gluten-containing recipe was available in the *Diet*

Planner. For those cases a gluten-free recipe was obtained from recipe databases or various blogs.¹

Gluten-free recipes registered and detailed list of contents were used for other participants who reported consuming a matching dish. When no available portion size was accessible in the *Diet Planner*, the portion size for a similar food item or meal was used. The booklet 'Weights and Measures for Foods' was used as a supplementary guide for estimating household measurements if data on a household measure for a given food were not available in the *Diet Planner* (113).

All food diaries were controlled for gluten-containing foods and dietary supplements. Cod-liver oil was the only supplement calculated when entering the food diaries in the *Diet Planner*. All supplements were registered as 'use' and 'do not use' supplements. Meal replacements were included in the analysis of food diaries, as the energy intake would otherwise have been lower than actual intake.

3.5.4 Validity of reported food intake

Under-reporting of dietary intake was determined using the revised Goldberg cut-off method (115). This method is based on the principle that energy intake (EI) and energy expenditure (EE) is in equilibrium (EI=EE). Energy expenditure is equal to the energy requirements, which can be estimated as multiples of basal metabolic rate (BMR) and physical activity level (PAL). This gives the equation $EI/BMR = PAL$. The principle behind Goldberg's cut-offs is that an estimated PAL could be evaluated against an expected PAL for a particular population. The revised Goldberg cut-off values (PALs) are based on estimated 95 % confidence limits of EI. The values of these cut-off points vary according to PAL for the actual group, number of people in the group and days of food recording.

The mean ratio EI:BMR for NCGS females and males gave information to estimate the PAL. Mean BMR was calculated by the Mifflin-St. Jeor equation (116). Degree of under-reporting at group level was determined by comparing the estimated PAL (mean EI/mean BMR) with the lower 95 % confidence cut-off PAL from Goldberg equation appropriate for this study.

¹ Blogs and food recipe databases used were: Matprat.no, Mytaste.no, Trinesmatblogg.no, Snadderutengluten.no, Utenglutenblogg.no

3.5.5 Intake of nutrients compared to recommendations

To evaluate quality of the diet, the intake of proteins, fat, carbohydrates and micronutrients was compared to Nordic Nutrition Recommendation 2012 (NNR12) (117). The recommended intakes of macronutrients have a wide range. To get a more defined comparison, our NCGS population was compared with mean recommendations for energy-giving nutrients on group-level (117).

3.5.6 Nutrient density

Quality of the diet was evaluated by comparing nutrient density of reported intakes (nutrient eaten/energy intake, MJ) with nutrient density of reference intakes (recommended intake (RI)/reference energy intakes, MJ). Reference energy intakes were those given in NNR12 for females and males 31 – 60 years with PAL of 1.6 (sedentary lifestyle and limited activity at leisure time) (117). Nutrient density per 10 MJ for all NCGS patients completing food diaries were calculated for comparison with nutrient density in the average Norwegian population (Norkost 3) (88).

3.5.7 Gluten-free diet adherence and literacy

Adherence to GFD was measured using an adherence questionnaire² developed at Rikshospitalet for coeliac patients (Appendix 5) (118). It had been developed using results from focus groups with CD patients. Leffler`s Coeliac Dietary Adherence Test and Van Hee`s Gluten-free Dietary Habits questionnaire were both used as guidance literature (119, 120). The adherence questionnaire was based on strategies used by CD patients to avoid eating gluten. This questionnaire was found to have good specificity, being useful for recognizing adherence. The internal consistency was also found to be good.

The questionnaire consisted of three sections. Eleven questions from the second section that concerned compliance to GFD were deemed most suitable for determining GFD adherence in NCGS patients. All questions had five response categories, scored from 1 to 5, where a lower score indicated better adherence. A sum score of 20 points out of a maximum 55 was set as cut-off score for inadequate adherence. This gave a corresponding percentage cut-off score as for the original adherence questionnaire, where cut-off was 27 out of 75 points.

² The Martine questionnaire, developed by Marie Wegge Nilsen, 2012.

Three questions were added to the adherence questionnaire. The first question was a control for inclusion criteria, assessing the degree of GFD adherence the past six months. The other two concerned intake of ordinary beer, as well as bread, oats and spelt. The added questions were statistically described using numbers and percentages, and did not contribute to the total score of the adherence questionnaire. The food diary was checked for gluten-containing foods and served as a control for gluten-free diet adherence together with the knowledge test.

A knowledge test was specifically developed to test participants' nutrition literacy regarding GFD (121), and complimented the adherence questionnaire. The test contained 26 basic questions related to gluten-free products (Appendix 6). The selected questions were approved by Gry Skodje (dietician and PhD student at OUH Rikshospitalet), Christine Henriksen (dietician, PhD in clinical nutrition at University of Oslo) and Knut Lundin (consultant and gastroenterologist at OUH Rikshospitalet).

3.6 Clinical symptoms

3.6.1 Gastrointestinal symptoms

Gastrointestinal symptoms were scored with Gastrointestinal Rating Scale for Irritable Bowel Syndrome (GSRS-IBS), which is a valid and reliable symptom questionnaire developed for patients with IBS (Appendix 7) (122). It is used for monitoring changes in IBS symptoms in clinical settings and measuring the effect of treatment. At OUH Rikshospitalet the questionnaire is used with IBS, CD and NCGS patients. It has also been used in another clinical study on a NCGS population (75).

The self-assessed symptom questionnaire has 13 items, each evaluated on a 7-point Likert scale (1–7), from 'no symptom' to 'very serious symptom', and should reflect symptoms experienced the last seven days. The GSRS-IBS contained five clusters of symptoms: pain, bloating, constipation, diarrhoea and satiety (122). In this study, only the total score was calculated, matching the clinical application of GSRS-IBS at OUH Rikshospitalet. The method of using the total score has also been reported in a study on CD patients by Leffler et al. (123). GSRS-IBS was used to evaluate whether patients were in control of their gastrointestinal symptoms together with visual analogue scales (VAS) for gastrointestinal symptoms.

A 7-day visual analogue scale (VAS) -diary of 100 mm was developed to measure gastrointestinal symptoms (Appendix 8). The VAS diary measured intensity of pain, bloating, flatulence, nausea, stool pattern and overall gastrointestinal symptoms, with 0 denoting no symptom and 100 the worst symptom. The VAS was constructed by Gry Skodje (dietitian and PhD student at OUH Rikshospitalet) and by the author of this thesis based on the method developed by Brottveit et al. (75), and the methods for evaluating symptoms in the NCGS gluten-challenge studies conducted by Biesiekierski et al. (24, 25). VAS is similar to the numeric rating scale (NRS) described in the diagnostic protocol of NCGS according to the Salerno Experts' Criteria (8).

3.6.2 Fatigue

To measure fatigue, a modified version of the short-form Giessen Subjective Complaint List (GBB) was utilized (124). The GBB, developed in 1994, has been developed and validated in German (125). The questionnaire consists of 24 items defining four sub-scales (exhaustion, gastric symptoms, pain in the limbs, and heart complaints) (124). Based on recommendations from psychiatrist Birgitte Boye (OUH Radiumhospitalet), the six complaints belonging to the sub-scale 'exhaustion' were used: weakness, need for sleep, exhaustion, tiredness, dizziness and fatigue (Appendix 9) (126). This section of the questionnaire was translated from German into Norwegian by Olav Vassend, professor at the Department of Psychology, University of Oslo. Each question can be scored on a Likert scale from 0 (no complaint) to 4 (severely affected), and the six items are summed to measure the overall level of fatigue. Scores within the questionnaire range from 0 to 24, with a higher score indicating a greater level of fatigue.

The severity of fatigue was also recorded with a VAS for each sub-scale of the section of GBB measuring exhaustion (Appendix 10). The commonly reported extra-intestinal symptoms such as concentration difficulties, joint/muscle pain, depression, numbness, tingling in hands and feet were also added to this GBB-VAS questionnaire (127).

3.6.3 Depression

Depression was measured by the Beck Depression Inventory – second version (BDI-II), a valid and reliable self-administered questionnaire that measures degree of depression in youth over 13 years of age, and adults. BDI-II was first published in 1996, revised from the original BDI published in 1961 (128, 129). A Norwegian translation published in 2005 was utilized in

this thesis (Appendix 11). The translation to Norwegian is performed through a back translation procedure and Pearson Assessment has the rights for the Norwegian version. In Norway, BDI-II is used to screen people for depression (130).

BDI-II is composed of 21 items concerning symptom of depression, which are scored on a Likert scale from 0 (not affected) to 3 (severely affected). The original BDI-II was meant to reflect the two last weeks. For the purpose of this thesis, BDI-II was modified to describe symptoms in the course of the past week. The total score can be separated into different threshold values of depression: minimal depression (0–13) mild depression (14–19), moderate depression (20–28) and severe depression (29–63) (129).

If two statements of an item had been selected the higher score was calculated. An empty item was scored with the mean item score of BDI-II. BDI-II questionnaires with more than 50 % missing answers were excluded from the analysis (129).

3.6.4 Subjective health complaints

Somatic and psychological complaints experienced by NCGS patients were measured through completion of the validated Subjective Health Complaints inventory (SHC) (131). SHC is a solid tool to measure general well-being or absence of such. It also can be valuable in conditions where no diagnostic system is available (131). The original questionnaire was developed for registration of symptoms during the past 30 days, but was modified to 7 days for the purpose of this study (Appendix 12). The instrument consists of a list of 29 common health complaints, with severity scored on a four-point scale from 0 (no complaints) to 3 (severe complaints) (131). There is no cut-off for the total score of complaints. If the participants identified more than one complaint, they were also asked to specify which they considered to be the worst (131, 132).

Complaints cluster into five sub-scales:

1. Musculoskeletal symptoms: headache, neck pain, shoulder pain, pain in arms, pain in upper back, lower back pain, migraine, leg pain.
2. Pseudo-neurological symptoms: palpitations, heat flushes, sleep problems, tiredness, dizziness, anxiety, sadness/depression.

3. Gastrointestinal: heartburn, stomach discomfort, ulcer/non-ulcer dyspepsia, stomach pain, gas discomfort, diarrhoea, constipation
4. Allergic complaints: asthma, breathing difficulties, eczema, allergies, chest pain.
5. Flu-like complaints: cold, influenza, cough.

In this study responses to the SHC were calculated in three separate ways. Firstly, the total symptom load for each sub-scale was calculated, with a sum score ranging from 0 to 87. Secondly, responses to each complaint were categorized into absent (score 0) or present (score 1–3), and the prevalence of complaints within the five sub-scales was calculated. Lastly, the prevalence of the most severe complaint as identified by each participant was calculated. For missing values, the mean values of the items within the same scale for that individual were imputed (131). If more than 50 % of values were missing within a sub-scale, that sub-scale was considered missing for that individual (131).

3.7 Health-related quality of life

HRQoL was measured by the Short Form-36 questionnaire (SF-36), a generic, multi-purpose, short-form health survey (133). The original questionnaire reflects the past four weeks; however, we used a modified version which reflects only the previous week (Appendix 13). SF-36 has been translated into Norwegian and is validated in Norway (134).

The survey contains eight multi-item scales for self-assessment of the following health concepts: limitations in physical functioning due to health issues; limitations in normal role activities because of physical health problems; bodily pain; general health perceptions; vitality (energy level and fatigue); limitations in social activities due to physical or emotional problems; limitations in usual role activities because of emotional problems; and general mental health (psychological distress/well-being) (135).

The SF-36 also contains one item referred to as ‘health transition’, which is not used to score any of the eight multi-item scales. This item provides valuable information as regards change in perceived health status over the previous year, e.g. change between pre- and post-GFD (136).

The SF-36 items were scored according to published scoring procedures (136). An SPSS syntax developed by Jon Håvard Loge was then utilized to transform the SF-36 items into scales (137). Final scores for each scale as well as the health transition items were interpreted so that a higher score indicated better perceived health (136, 137). All scales were transformed into scores ranging from 0 to 100, except for the social functioning scale. This scale yielded a maximum score of 112.5, as question 10 (item 32) in the SF-36 version applied in this study had an additional response category.

3.8 Statistical analysis

Statistical analysis was performed using the SPSS version 22 (IBM Corp, Released 2013, Armonk, NY).

Analyses in this thesis are mainly descriptive statistics, using frequencies and average values to sort out data on characteristics, nutrition and symptoms. Normally distributed data are presented with means and standard deviations; abnormally distributed data are presented as median and quartiles 25th and 75th percentiles (Q₁, Q₃). Categorical data are described by total frequencies and percentages, and analysed by Pearson's chi-square test. The paired t-test is used for normally distributed data and the Mann-Whitney U test for non-parametric data when checking for differences between female and male results. All tests are two-sided, and a p-value of <0.05 was considered significant. Correlations have been checked with Spearman's correlation coefficient (p<0.001), due to the small sample size and correction for outliers. Nutrient intake in NCGS patients was descriptively compared to NNR12.

Sample size was calculated for the challenge study based on 80 % power to find a true clinical significant difference in GSRS-IBS score in response to the challenge. This gave a demand for 49 participants. With a calculated withdrawal of 30 %, the study needed to enrol 66 participants.

4 Results

4.1 Recruitment

In total, 233 patients with suspected NCGS were screened. Of these patients, 161 were not eligible to participate due to the following reasons: CD not being excluded; nut allergy; lived too far from OUH; symptomatic on GFD; non-compliant with GFD; unwillingness to participate; pregnant/trying/lactating; and HLA type not available. Of the 72 eligible for the study, four withdrew from the study. During the study, one patient was excluded due to positive duodenal biopsy for coeliac disease, and another had her baseline consultation after the limited data collection period of this study. The final study population thus consisted of 66 participants (Figure 4). Results from baseline described NCGS patients while on gluten-free diets, and should reflect well-controlled symptoms.

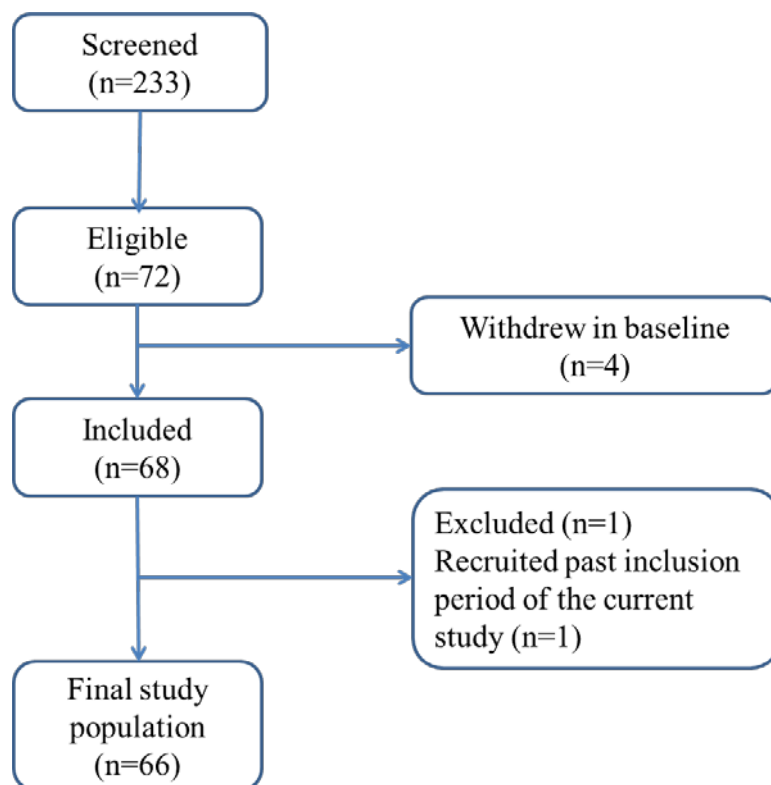


Figure 5. Flow chart of inclusion and exclusion of participants

4.2 Characteristics

General characteristics of the study sample are shown in Table 3. Patients were between 21 and 72 years old, with an average age of 44, and most of them were females. As to reported work situation, 16 % were disabled, and could be assumed to be receiving disability benefits. In addition 5 % were students, possibly not employed full time, and 3 % were currently without work. Sixty percent of the NCGS patients had a sedentary work situation, and half of the study patients reported that they engaged in some form of physical activity for two to three hours a week. Only 6 % reported that they were smokers. Use of dietary supplements was reported by 45 % of the patients (see Appendix 14). Forty-seven patients (71 %) reported practising other food avoidances apart from gluten, including dairy products (79 %), one or more FODMAP containing food (56 %) and sugar (16 %). 47 % of patients had unique food item avoidances (see Appendix 15). Alcohol consumption was reported in 85 % of the NCGS sample, and was evaluated to be moderate.

Table 3. Patient characteristics. Mean (SD) or number (%), n=66

Age in months, mean (SD)	43.7 (11)
	n (%)
Gender	
Women	58 (88)
Men	8 (12)
Work situation	
Student	3 (5)
Seeking work/laid off	2 (3)
Disabled	11 (16)
Public sector	22 (33)
Private sector	20 (30)
Self-employed	2 (3)
Other	6 (9)
Activity level	
Activity level at work:	
Bed-ridden/inactive	2 (3)
Sedentary work	39 (63)
Standing work	17 (27)
Physical work	3 (5)
Activity level, leisure time: ^a	
Low activity level	16 (24)
Active	33 (50)
Very active	17 (26)
Smoke	4 (6)
Take supplements^b	25 (46)
Use meal replacements^c	2 (4)
Other food avoidances	43 (65)
Avoid dairy products	34 (79)
Avoid intake of high FODMAP foods ^d	24 (56)
Avoid intake of sugar	7 (16)
Less common food avoidances ^e	22 (51)
Drink alcohol	56 (85)

Abbreviations: SD, standard deviation.

^aLow, < 2 hours activity/week; active, 2–3 h/week; very active, > 3 h/week

^bSupplements recorded in the food diary; includes both dietary- and non-dietary supplements, n=56

^c9 missing for utilization of meal replacements, n=56

^dNot including dairy products

^eLess common food avoidances are listed in Appendix 15

4.2.1 Medical characteristics

Medical history obtained from the NCGS patients are presented in Table 4. Investigation of IBS prior to the study was performed in 34 % of NCGS patients. Results from questioning about Rome III criteria for IBS showed that 30 % fulfilled criteria for IBS. NCGS patients fulfilling criteria for IBS reported significantly higher gastrointestinal symptoms than those who did not fulfil IBS criteria (GSRs-IBS median score: 36 (27, 44) versus 24 (19, 33); Mann Whitney U test: $p=0.003$). Of those fulfilling the criteria for IBS, 80 % were positive to either HLA-DQ2 or HLA-DQ8 a significant association compared to those who were negative (Chi-square: $p=0.028$). About one fourth and one fifth of the NCGS patients reported having family members with CD or NCGS, respectively. Comorbidities were present in 68 % of the study sample, with thyroid disease the most frequent (30 %). Less common comorbidities are detailed in Appendix 16.

Table 4. Medical characteristics of study sample. Mean (SD) or number (%), n=66

Medical measurements^a	
Systolic blood pressure, mmHg mean (SD)	127.4 (15.7)
Diastolic blood pressure, mmHg mean (SD)	75.7 (10.3)
Heart rate, bpm ^b mean (SD)	68.3 (9.8)
Physical examination ^c n (%)	
No abnormalities	59 (97)
Clinical history	
Previous investigated for IBS ^d n (%)	22 (34)
Fulfilled criteria for IBS ^e n (%)	20 (30)
Family member with CD n (%)	17 (26)
Family member with NCGS n (%)	11 (17)
Additional diseases n (%)	45 (68)
1 disease	22 (33)
2 diseases	12 (18)
> 2 diseases	11 (17)
Thyroid disease n (%)	20 (30)

Abbreviations: SD, standard deviation; (Q₁, Q₃), 25th-75th percentile; IBS, irritable bowel syndrome; GFD, gluten-free diet.

^a5 missing for medical measurements, n=61

^b6 missing for heart rate, n=60

^cPhysical examination for cor/pulm/abdomen. 5 missing, n=61

^d1 missing for investigated for IBS, n=65

^eRome III criteria for IBS

Biopsy, histology and coeliac serology

Investigation for CD by duodenal gastroscopy prior to the study was performed in 72 % of NCGS patients, whereof 85 % consumed gluten before the gastroscopy (Table 5). Fifty-seven NCGS patients followed gastroscopy per protocol, and twelve refused the biopsy: thus, 89 % performed gastroscopy. Increased levels of IELs were seen in 35 % of the NCGS patients taking biopsy. Among the patients with heightened IELs levels, 10 % had >25 IELs per enterocytes with normal crypts and villi, giving Marsh grade 1.

Results from serology showed that 61 % of the patients had the genes susceptible for CD: HLA-DQ2 or HLA-DQ8, with HLA-DQ2 the most frequent gene presented. None of the patients had increased levels of IgA autoantibodies to transglutaminase-2 (TG2), but nine patients (14 %) showed elevated amounts of IgG to deaminated gliadin peptide (DGP) (>5 Units).

Table 5. Results from CD-related serology and duodenal gastroscopies.
Number (%), n=66

	n (%)
Serological findings:	
Positive test for HLA-DQ2 and DQ8:	40 (61)
HLA-DQ2 positive	23 (35)
HLA-DQ8 positive	17 (26)
Autoantibodies: ^a	
IgA-TG2	0 (0)
IgG-DGP	9 (14)
Previous coeliac investigation by gastroscopy:	
Performed gastroscopy ^b	47 (72)
Intake of gluten before gastroscopy ^c	40 (85)
Gastroscopy performed in the study:^d	
Increased amounts of IELs	18 (35)
Marsh 0	41 (79)
Marsh ^e 1	5 (10)

Abbreviations: CD, coeliac disease; TG2, tissue transglutaminase-2; DGP, deaminated gliadin peptide; IELs, intraepithelial lymphocytes; EC, epithelial cell.

^a2 missing for autoantibodies

^b1 missing for performed gastroscopy when investigated for coeliac disease, n=65

^c2 missing for gluten consumed before gastroscopy, n=64

^d5 missing for performed gastroscopy in the study, n=52

^eMarsh 1: > 25 IELs/100 EC

4.3 Nutritional status

4.3.1 Body mass index

Average BMI was within normal weight, although in the upper normal range (24.8 kg/m²): 37 % were in the overweight range, 11 % were in the obese range and 5 % were in the underweight range (Table 6). The proportion of patients in the obese and overweight range added together (48 %) was similar to the number of participants in the normal range (48 %).

Table 6. Nutritional status of study sample by BMI. Mean (SD), number (%), n=66

Weight, (kg) mean (SD)	71 (14)
Height, (cm) mean (SD)	169 (7)
BMI ^a , (kg/m ²) mean (SD)	25 (4)
Underweight (< 18.5 kg/m ²) n (%)	3 (5)
Normal (18.5-24.9 kg/m ²) n (%)	31 (48)
Overweight (25.0-29.9 kg/m ²), n (%)	24 (37)
Obese (> 30.0 kg/m ²), n (%)	7 (11)

Abbreviations: SD, standard deviation; BMI, body mass index.

^aWHO cut-off for BMI

4.3.2 Nutritional biomarkers

Results from assessment of nutritional biomarkers are shown in Table 7. The results are summarized in categories for average values (mean and *median*) and number and percentages of patients that fell below and above reference values. The biomarkers with values below reference values were TSH (18 %), iron (3 %), and transferrin (3 %). Values above reference values were seen for albumin (32 %), vitamin B12 (16 %) and PTH (12 %). Results for D vitamin revealed that 9.5 % of NCGS patients had 25-OH vitamin D below 50 nmol/L (suboptimal status), but no one had values below 25 nmol/L (deficiency). Laboratory data separated on gender and reference values are presented in Appendix 17.

Table 7. Nutritional status by laboratory data, presented as average values and number of NCGS subjects within, below or above reference values. Mean (SD), median (Q₁, Q₃)^a and number (%). N=66

Nutritional biomarkers	Average values (n=66)		Below reference value	Above reference value
	Mean (SD)	Median (Q ₁ , Q ₃)	n (%)	n (%)
Haemoglobin (g/dL)	13.95 (1.04)	13.8 (13.3, 14.7)	1 (2)	3 (5)
Iron (µmol/L)	17.36 (5.57)	<i>16.0 (13.0, 21.0)</i>	2 (3)	1 (2)
Ferritin (µg/L)	88.46 (59.64)	<i>71.5 (45.8, 116.8)</i>	0 (0)	3 (5)
Transferrin (g/L)	2.61 (0.35)	2.6 (2.4, 2.8)	2 (3)	4 (6)
Free calcium (mmol/L) ^b	1.26 (0.13)	<i>1.24 (1.2, 1.3)</i>	0 (0)	0 (0)
Cobolamine, B ₁₂ (pmol/L) ^c	462.03 (224.0)	<i>402.5 (288.8, 584.3)</i>	1 (2)	10 (16)
Folic acid, B ₉ (nmol/L)	26.04 (9.5)	<i>26.0 (17.8, 33.0)</i>	0 (0)	0 (0)
25-hydroxy vitamin D (nmol/L) ^d	69.21 (18.8)	<i>68.0 (57.0, 79.0)</i>	1 (2)	0 (0)
HbA1c (%) ^d	5.30 (0.5)	<i>5.2 (5.0, 5.5)</i>	0 (0)	1 (2)
TSH (x10E-3 IU/L)	1.34 (0.9)	<i>1.3 (0.7, 1.8)</i>	12 (18)	1 (2)
FT4 (pmol/L)	15.39 (2.9)	<i>15.0 (14.0, 17.0)</i>	0 (0)	2 (3)
PTH (pmol/L) ^b	4.97 (2.5)	<i>4.2 (3.5, 6.0)</i>	0 (0)	8 (12)

Abbreviations: HbA1c, glycated haemoglobin A1c; TSH, thyroidea-stimulating hormone; FT4, free thyroxin; PTH, parathyroidea hormone. Values with *italic font* are non-parametric, median should be readed.

^aQ1 25th percentile, Q3 75th percentile

^b1 missing for free. Calcium and PTH, n=65

^c2 missing for B12, n=63

^d3 missing for 25-hydroxy D vitamin and HbA1c, n=63

4.3.3 Determining under-reporting

Goldberg's cut-off PAL was applied to NCGS study sample (138), comprising of about 50 patients completing a 7-day food record to estimates a cut-off PAL. This gave a cut-off PAL of 1.47, the lower 95 % confidence limit. The ratio between energy intake and BMR in the study sample was 1.30 and 1.32 for females (n=48) and males (n=8), respectively.

Comparison of these PALs against the chosen Goldberg cut-off for under-reporting (PAL: 1.47) indicated under-reporting of energy in NCGS patients (138).

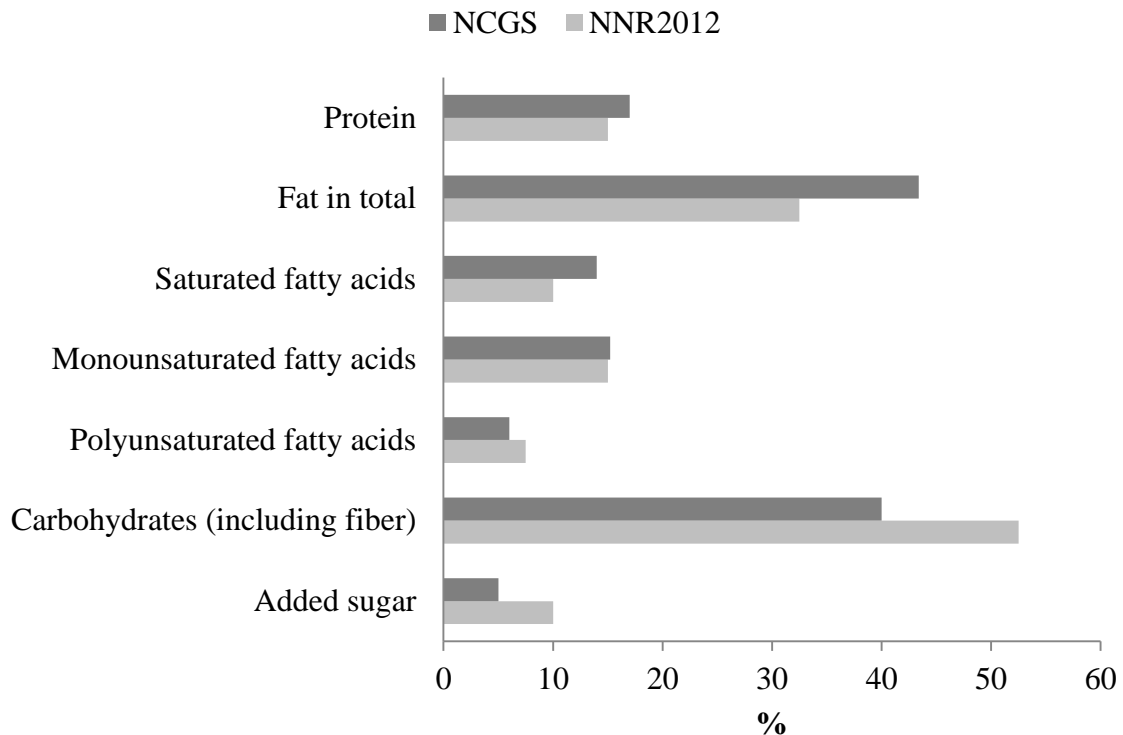
4.3.4 Comparison of dietary intake with Nordic Nutrition Recommendations 2012

The analysis included a total of 56 food diaries. One food diary was missing; one of the 66 participants was excluded; and eight diaries were not included because they were outside the time frame of the master thesis. Mean energy intake was 1774 kcal for women and 2259 kcal for men (Table 9) – a significant difference between females and males (Mann-Whitney U test: $p=0.009$). The NNR12 reference values are 2102 kcal and 2638 kcal for females and males respectively, 31-60 years old and with an average PAL of 1.6 (117).

Macronutrients

Intakes of macronutrients are presented as energy proportion of the total energy intake, E %, as recommendations for macronutrients are similar for both genders. The results for macronutrients in E % showed no significant difference between females and males.

Intake of macronutrients is shown in Figure 6 and detailed in Appendix 18. The provided mean energy from fat was 43 % and higher than recommended, range 25–40 %. Compared to recommendations at group-level, fat intake was 11 % higher than recommended intake of 33 %. Median energy from saturated fat was 14 %, exceeding the reference threshold by 40 %. By contrast, median intake of carbohydrates was 40 %, lower than the recommended range 45–60 % and deviated from recommended level advised for groups by 13 %. Median intake of dietary fibre was 19 g, a discrepancy of 6 g from the lower recommended limit (25-35 g) and 4 g below the recommended fibre intake for NCGS patients based on energy intake (3 g/240 kcal: 23 g) (114). Daily intake of added sugar was lower than the upper recommended limit of 10 % (median: 5 %).



Abbreviations: NCGS, non-coeliac gluten sensitivity; NNR12, Nordic Nutrition Recommendations 2012. N=56. Mean values: fat n total and monounsaturated fatty acids, median: protein, saturated fatty acids, polyunsaturated fatty acids, carbohydrates and added sugar.

Figure 6. Intake of nutrients in energy percent compared to recommendations for groups by NNR12.

Micronutrients

Table 8 shows the micronutrient intake of the study patients. Due to different recommendations for females and males these results are presented separately. Dietary supplements are not included, with exception for cod liver oil, though meal replacements are within the calculations. Females and males reported significant difference in niacin ($p=0.013$) and vitamin B₆ ($p=0.029$), tested with Mann-Whitney U tests. For other micronutrients, no differences were seen. Intakes of micronutrients are presented as median.

Females had an intake of calcium of 694 mg, which is 106 mg from the recommended level. Inadequate iodine intake was found, with an intake of 76 µg – only meeting 51 % of recommended value. This was also the case for iron, where the intake was 7.9 mg, equivalent to 53 % of the optimum intake. Female NCGS patients had an insufficient intake of vitamin D

of 6.7 µg. This was seen for folic acid as well with an intake of 208 µg. However, intake of vitamin C was 22 mg above reference value (96 mg), and intake of vitamin B₁₂ was 62 % above recommended values (5.2 µg).

The male patients had an inadequate intake of calcium of 579 mg. Intake of iodine was 62 µg, only 41 % of the recommended level. Intake of vitamin D was 5.8 µg, indicating insufficiency, as was the case for folic acid (209 µg) and vitamin A (584 RAE) as well. By contrast, intake of vitamin C was 89 mg, exceeding reference value with 14 mg, and intake of vitamin B₁₂ was 65 % above recommended value (5.7 µg). One male patient had a daily intake of 65.3 mg of iron (due to meal replacement containing 27 mg iron/100 g), giving a high total mean intake of 16 mg, though this did not affect median which is the value to be interpreted for iron: If this participant was excluded from the iron analysis, the median was 8.5 (7, 11), similar to median when including this participant, median of 9.3 (7, 12). The iron intake in men was considered to be adequate.

Table 8. Average daily intake of energy and micronutrients^a in NCGS patients compared to NNR12, for both females and males. Mean (SD) and median (Q₁, Q₃)^b.

Intake of energy and micronutrients	NCGS Females (n=48)			NCGS Males (n=8)		
	Mean (SD)	Median (Q ₁ , Q ₃) ^b	NNR12	Mean (SD)	Median (Q ₁ , Q ₃) ^b	NNR12
kJ	7415 (1526)	7389 (6350, 8501)		9418 (2244)	9352 (7555, 9942)	
Kcal	1774 (366)	1769 (1516, 2032)		2259 (545)	2249 (1808, 2379)	
Cholesterol	328 (176)	271 (214, 394)	<300	373 (252)	329 (184, 510)	<300
Vitamin A	759 (565)	620 (458, 875)	700	711 (320)	584 (508, 826)	900
Vitamin D (µg)	7.4 (5.3)	6.7 (3.5, 9.4)	10	8.5 (8.6)	5.8 (5.1, 6.5)	10
Vitamin E (α-)	14 (6)	13 (10, 17)	8	18 (12)	12 (11, 25)	10
Thiamine (mg)	1.2 (0.4)	1.1 (0.8, 1.4)	1.1	1.5 (0.6)	1.3 (1.1, 1.6)	1.3
Riboflavin	1.6 (0.6)	1.6 (1.2, 1.9)	1.2	1.6 (0.4)	1.6 (1.3, 1.7)	1.5
Niacin (mg)	16.9 (5.5)	16.2 (13.4, 19.2)		25.3 (14.2)	21.1 (17.4, 26.8)	
Vitamin B6	1.6 (0.5)	1.5 (1.3, 1.8)	1.2	2.3 (1.2)	2.0 (1.6, 2.7)	1.5
Vitamin B ₁₂	5.3 (2.0)	5.2 (3.6, 6.8)	2	5.2 (2.1)	5.7 (2.9, 7.1)	2
Folic acid (µg)	224 (76)	208 (177, 257)	300 ^h	290 (228)	209 (153, 340)	300
Vitamin C (mg)	97 (50)	96 (51, 125)	75	109 (105)	89 (46, 114)	75
Calcium (mg)	723 (323)	694 (443, 927)	800	607 (315)	579 (360, 764)	800
Iron (mg)	9 (3)	7.9 (6, 10)	15	16 (20)	9.3 (7, 11)	9
Magnesium	290 (103)	279 (223, 333)	280	434 (386)	277 (211, 523)	350
Sodium (g)	2.1 (0.8)	1.9 (1.6, 2.5)	2.3	2.0 (0.8)	2.1 (1.7, 2.8)	2.3
Potassium (g)	3.1 (0.9)	2.9 (2.5, 3.7)	3.1	3.6 (1.9)	3.1 (2.4, 4.3)	3.5
Zinc (mg)	9 (3)	8 (7, 10)	7	11 (6)	8 (8, 13)	9
Selenium (µg)	52 (36)	43 (30, 65)	50	59 (25)	52 (39, 77)	60
Copper (mg)	1.2 (0.5)	1.1 (0.8, 1.4)	0.9	1.7 (1.5)	1.1 (0.8, 1.9)	0.9
Phosphorus	1259 (346)	1244 (1049, 1468)	600	1490 (668)	1371 (1066, 1867)	600
Iodine (µg)	81 (52)	76 (41, 106)	150	89 (75)	62 (38, 123)	150

Abbreviations: NCGS: non-coeliac gluten-sensitivity, NNR12: Nordic Nutrition Recommendations 2012; SD, standard deviation. Values in *italic font* are non-parametric, median should be readed. Values in bold are statistical different intake between women and men, tested by Mann-Whitney U test (p<0.05): energy intake; p=0.009, niacin; p=0.013, vitamin B₆; p=0.028.

^aResults are based on a 7-day food diary. Supplements are not included, except for cod-liver oil.

^bQ₁ 25th percentile, Q₃ 75th percentile

^cRAE, retinol activated equivalents: 1 µg retinol=12 µg beta-carotene

^dα-TE, alpha-tocopherol equivalents: 1 alpha-tocopherol equivalent=1 mg RRR-alpha-tocopherol

4.3.5 Nutrient density

Results from calculations of nutrient density can be found in Appendix 19. The calculated nutrient densities for vitamins and minerals are separated by gender when compared to the reference intakes. The nutrient density for the total NCGS sample is compared to the average Norwegian population by nutrients density per 10 MJ. Results are based on the 56 NCGS patients who completed their food diaries and are presented in Table S1. Results from these analysis indicated that NCGS patients ate foods containing fewer nutrients than recommended and the overall diet quality was lower than the average Norwegian diet.

4.3.6 Gluten-free diet adherence

Results from evaluation of the gluten-free diet adherence are presented in Table 9. NCGS patients were found to have followed a GFD for a median of 19.5 months (1.6 years) prior to participation, ranging from 4.5 to 180 months. By mistake, one person was challenged before 6 months on GFD diet. Information about the GFD was obtained from a medical doctor in most cases (35 %), followed by other sources (20 %), internet (17 %), family member (14 %) and friends (9 %). Only 5 % of NCGS patients had been informed about GFD by a dietitian, thus 60 % and 40 % were classified as self-instructed and professionally instructed respectively. Analysis of the adherence questionnaire showed that NCGS patients did adhere to their gluten-free diets, giving a median score six points below the cut-off score for inadequate adherence (20 points). A high median knowledge score (24 of 26) support the adherence finding. When asked about their GFD adherence the past six months, 82 % answered that they had followed the diet all the time, while 19 % answered most of the time. Those who answered “most of the time”, often ascribed restaurant and holiday mishaps as the reasons for their unintended gluten exposures. In response to questions about intake of ordinary bread, ordinary oats and spelt flour, ‘yes’ was given only for intake of ordinary oats (5 %). Occasional oat intake was reported by 12 % of participants, whereas consumption of ordinary bread or spelt flour was uncommon.

Findings after controlling the food diaries for gluten-containing foods revealed that two participants had intake of either rye crisp-bread or barley porridge (by on one and two occasions, respectively), and 6 % reported consuming ordinary oats.

Table 9. Reported duration of the GFD and GFD adherence. Median (Q₁, Q₃)^a or number (%), n=66

Time on GFD in month median (Q₁, Q₃)	19.5 (10, 48)
Gluten-free diet information:	
Professionally instructed ^b	26 (40)
Self-instructed ^c	40 (60)
Adherence questionnaire^d median (Q₁, Q₃)	14 (13, 20)
Knowledge test^e median (Q₁, Q₃)	24 (22, 25)
Adherence the past six months	
All the time n (%)	53 (82)
Most of the time n (%)	12 (19)
Consumption of gluten-containing foods:	
Ordinary bread n (%)	0 (0)
Occasionally n (%)	1 (2)
Ordinary oats n (%)	3 (5)
Occasionally n (%)	8 (12)
Spelt flour n (%)	0 (0)
Occasionally n (%)	2 (3)
Registered gluten intake in food diary:^f	
Gluten-containing foods n (%)	2 (4)
Ordinary oats n (%)	4 (6)

Abbreviations: SD, standard deviation; GFD, gluten-free diet

^aQ₁ 25th percentile, Q₃ 75th percentile

^bIncludes instruction by a medical doctor (35 %) or a dietitian (5 %)

^cIncludes information obtained from other sources (20 %), internet (17 %), family member (14 %), friends (9 %)

^d1 missing for the adherence questionnaire, n=65

^e2 missing for knowledge test, n=64

^fDietary data available for n=56

4.4 Clinical symptoms

4.4.1 Gastrointestinal symptoms

Table 10 shows the median scores from Gastrointestinal Rating Scale-IBS, where median total score was 29 of 91. Gastrointestinal symptoms measured by VAS were hardly above 10 mm, indicating that most patients had control over gastrointestinal symptoms on GFD (Table 7) (71). Flatulence (13 mm), bloating (12 mm) and changing stool pattern (12 mm) were the most bothersome symptoms. Independent of these results, as mentioned earlier, 30 % of NCGS patients fulfilled the criteria for IBS, indicating that some patients were having symptoms despite being gluten-free, which raised the GSRS-IBS score.

Table 10. Median (Q₁, Q₃)^a gastrointestinal symptom scores measured by GSRS-IBS and VAS. N=64

	Scoring scale	
GSRS-IBS	13-91	29 (21,36)
VAS ^b		
Pain	0-100	5.6 (2.7, 19.9)
Bloating	0-100	12.1 (4.4, 27.6)
Flatulence	0-100	13.3 (5.6, 24.2)
Nausea	0-100	2.6 (0.1, 7.8)
Stool pattern ^c	0-100	11.7 (4.5, 38.7)
Total complaints ^d	0-100	8.7 (3.1, 22.2)

Abbreviations: GSRS-IBS, Gastrointestinal Rating Scale -Irritable Bowel Syndrome; VAS, visual analogue scale.

^aQ₁ 25th percentile, Q₃75th percentile

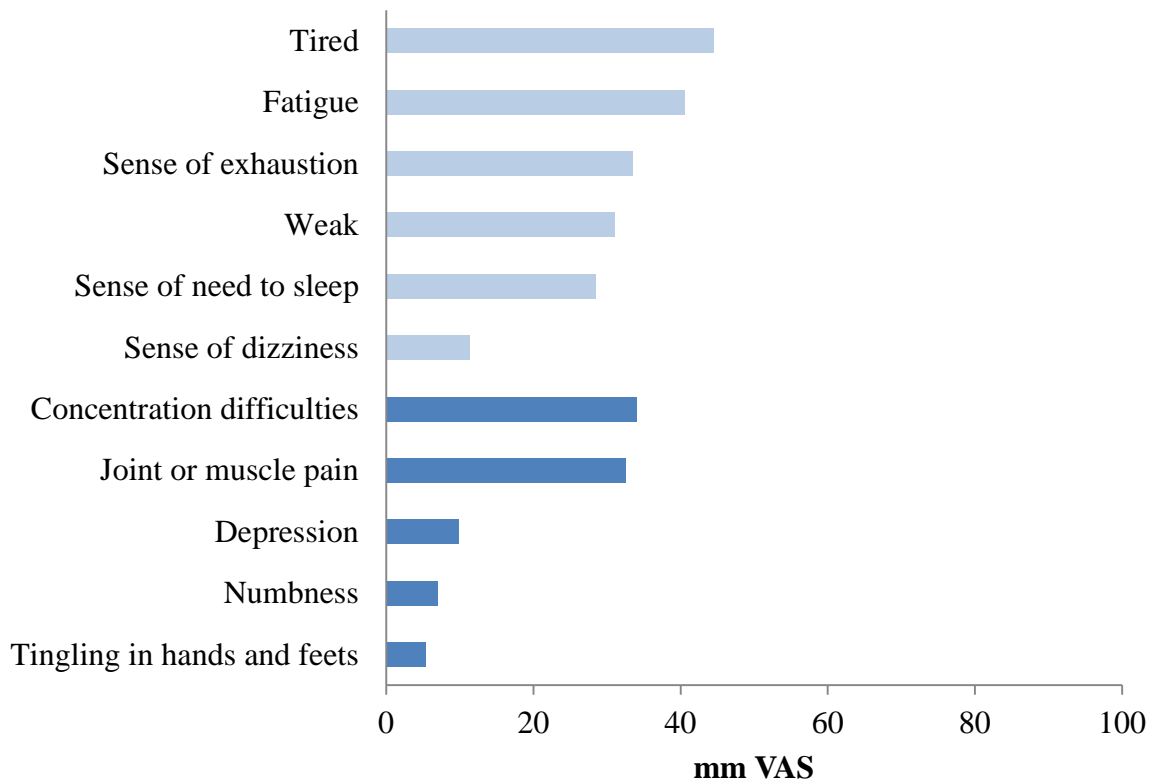
^b13 missing, n=53. VAS symptom diary is based on 7-day registration. 2 only recorded 5 and 6 days for all symptoms, respectively.

^c2 days of symptom recording missing for 1 participant.

^d1 day of symptom recording missing for 2 participants.

4.4.2 Fatigue

The median fatigue score from GBB was 9 (2, 14) of 24. Figure 7 shows the ranges of median scores from the GBB VAS for fatigue. The most common symptom was tiredness (44.5 (9.6, 71.8)), closely followed by fatigue (40.5 (9.0, 66.0)). The median total score by GBB gave a percentage score (38 %) of the total score similar to the scores from tiredness (45 %) and fatigue (41 %) by VAS. Other commonly reported extra-intestinal symptoms, measured by VAS, were concentration difficulties (34.0 (11.3, 56.4) and joint/muscle pain (32.5 (8.5, 60.6)).



Abbreviations: VAS, visual analogue scale. N=64. 1 missing for weak, n=63.

Figure 7. Reported fatigue and other extra-intestinal symptoms on a 100 mm VAS by NCGS patients. All values are presented in median.

4.4.3 Depression

The total sum score from BDI-II showed that NCGS participants had minimal depression, giving a median total score of 7.5 (3, 15). The depression score measured on a VAS was also low (10 mm) (Figure 7). As to degree of depression, 72 % were minimally depressed, whereas 20 % experienced mild, 5 % moderate and 3 % severe depression (Table 11). In other words, despite a low total score of BDI-II, a considerable proportion of participants had mild depression.

Table 11. Symptom of depression measured by BDI-II, n=64.

Scales of depression	n (%)
Minimal depression	46 (72)
Mild depression	13 (20)
Moderate depression	3 (5)
Severe depression	2 (3)

Abbreviation: BDI-II, Beck Depression Inventory - second version

4.4.4 Subjective health complaints

The results from the SHC questionnaire are shown in Table 12. Median total score was 13.5 of 87. The sub-scale comprising musculoskeletal symptoms was given the highest score, median 5.0 of 24. The overall low intensity of complaints indicates low severity of health complaints among NCGS patients, though many reported a low grade of at least one health problem in the five sub-scales. Concerning the question about the worst complaint out of 29 possible complaints, the extra-intestinal complaints tiredness (19 %) and headache (13 %) were most reported by participants. Neck pain and gas discomfort were reported to be most bothersome by an equal proportion of participants (11 %). Five percent reported no complaints, and diarrhoea was reported as problematic for only 2 % (Figure 8).

Table 12. Ranges of the results from intensity score of SHC (median (Q₁, Q₃)^a), and prevalence of subjects reporting at least one health complaint (score above 0) in the five sub-scales (number (%)). N=64.

	Scoring scale	
SHC total score	0-87	13.5 (8.3, 20.8)
Musculoskeletal	0-24	5.0 (3, 9)
Pseudoneurological	0-21	3.5 (1, 6.8)
Gastrointestinal	0-21	3.0 (2, 5)
Allergic	0-15	1.0 (0, 2)
Flu	0-6	0.0 (0, 1)
Prevalence of sub-scale complaints		
Musculoskeletal		60 (94)
Gastrointestinal		57 (89)
Pseudoneurological		57 (89)
Allergic		34 (53)
Flu		24 (38)

Abbreviations: SHC, subjective health complaints; SD, standard deviation.

^aQ₁ 25th percentile, Q₃ 75th percentile

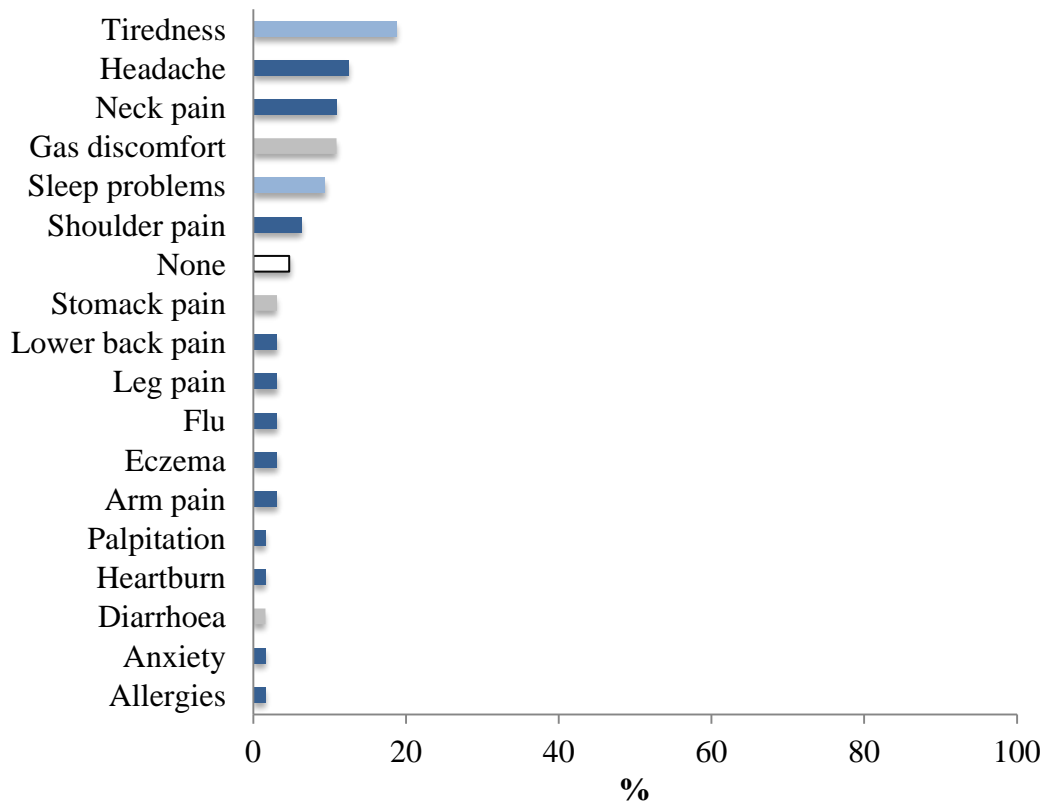
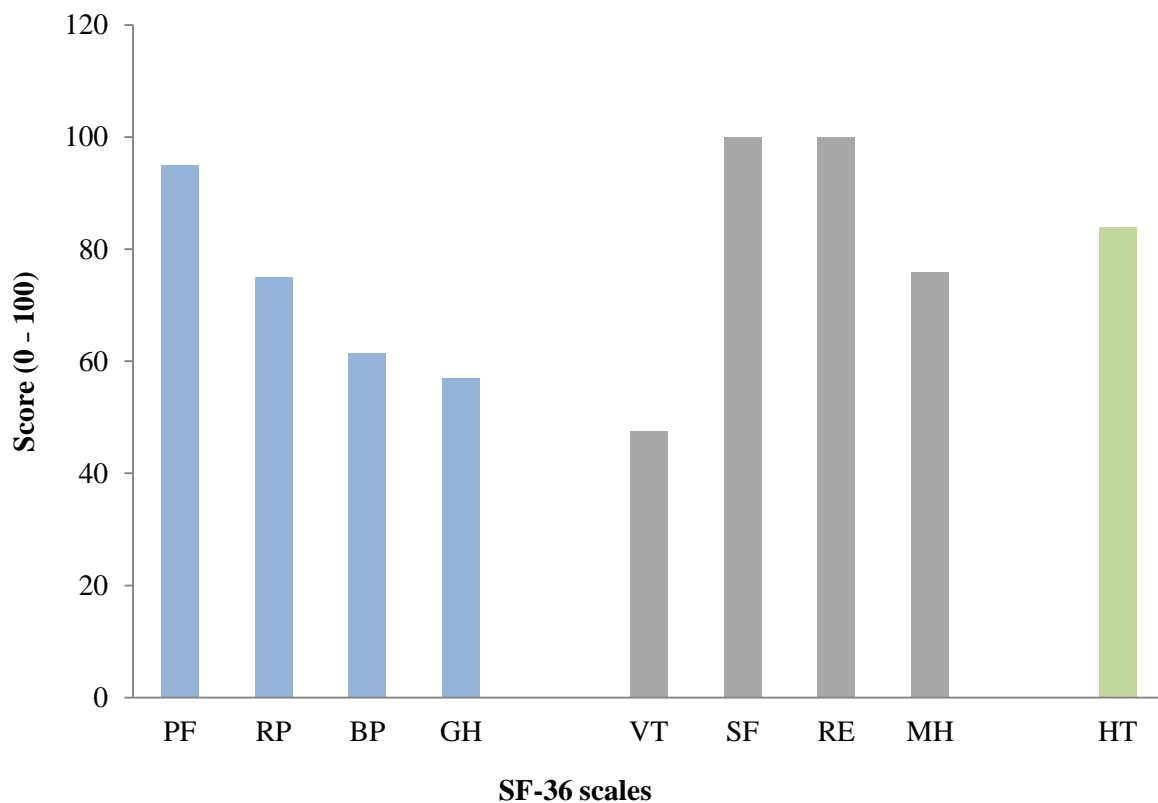


Figure 8. The most sever health complaints reported by NCGS patients measured by the questionnaire Subjective Health Complaints (SHC). Number (%), n=64.

4.5 Health-related quality of life

Figure 9 shows the SF-36 results. NCGS patients reported good health as regards social functioning (median: 100 (62.5, 112.5)), role emotional (median: 100 (66.7, 100)), and physical functioning (median: 95 (85, 100)) (Table 9). The lowest score concerned the scale energy and fatigue, termed 'vitality' (mean: 47.5 (25.4)). Patients' general health perceptions were not optimal (median: 57 (40, 82)) and some reported suffering from bodily pain (median: 61.5 (51, 78.5)). Moreover, limitations in daily activities due to reduced physical functioning (Role-Physical: median 75 (0, 100)) were present, in addition to some reduced mental health issues (mean: 75.9 (14.6)). However, the health transition item indicated a perceived health change toward the better during the past year.



Abbreviations: SF-36, short form 36; PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health; HT, Health Transition Item. Median values are shown for PF, RP, BP, GH, SF, RE and HT. Mean values are shown for VT and MH. N=64

Figure 9. Scores from the SF-36 scales in the NCGS sample.

5 Discussion

5.1 Summary of results

Results from nutritional assessment in NCGS patients showed that the average BMI was within the upper-normal range and nutritional deficiencies were hardly seen. The diet quality was not optimal: Total fat and saturated fat intake was higher than recommend, while intake of carbohydrates and dietary fibre was lower than recommended. Micronutrient intake was below the recommendations for, iodine, calcium, iron (in females), vitamin D and folic acid. Overall NCGS patients were found to have excellent adherence to the GFD. On this diet, both gastrointestinal and extra-intestinal symptoms were present. Patients reported extra-intestinal symptoms to be most bothersome, in regards of fatigue and mild depression. HRQoL was reduced for some aspects, especially for the scale comprising fatigue and loss of energy termed vitality.

5.2 Study population

All our participants were living in or near Oslo, and may therefore not be representative of the general NCGS population in Norway. In addition participation in a DBPC challenge is a time-consuming affair, which could result in full time employed individuals not wanting to enrol in this study: 16 % were disabled or on sick leave, 5 % were students and 3 % were seeking work/laid off. This may differentiate our NCGS study population from other NCGS populations. However, that many were disabled or on sick leave could be representative of general NCGS populations as they experience more clinical symptoms than the general healthy population (75), as described in IBS patients (97). The fact that participation was voluntary together with the possibility of financial support as an outcome of participation may have attracted patients with higher symptom burden, reducing the representativeness.

Patients recruited for the study were about 40 years of age. This is in line with another Norwegian NCGS population as well as several foreign NCGS populations (46, 59, 90). The female/male ratio was 7.3 to 1, somewhat higher than in the study by Volta and colleagues (46), perhaps due in part to a higher willingness among females to participate in large studies and to seek medical advice. It is generally accepted that females predominate among NCGS patients (46, 59, 68).

Almost two thirds of the study population (61 %) had either HLA-DQ2 or HLA-DQ8 haplotypes. Other studies of NCGS patients have reported a lower prevalence of these genes, closer to 50 % (39, 67, 81). This could be related to a higher prevalence of family members with CD (26 %) than found in other studies (approximately 13 %) (39, 71, 81, 139). It may well be that our study sample reported 'yes' for more distant family members with CD than other NCGS populations, as the prevalence of CD is reported to be similar (~1 %) across the NCGS study countries (12). Moreover, there is a chance of greater self-reported NCGS in people who have relatives with CD, as they can be more aware of the disease and the effects of gluten. Such individuals might be overrepresented in our study, perhaps due to announcing the study in the Norwegian Coeliac Society. In addition relatives of CD patients may be more interested in to participate in a clinical study as these individuals could actually have a gluten sensitive enteropathy, possibly possessing a relatively high symptom burden (140). Carroccio et al. (71) found a higher prevalence of relatives with CD in their wheat-sensitive group compared to the group with additional food hypersensitivity (14 % vs 2 %), and NCGS patients seemed to have a greater prevalence of family members with CD compared to CD patients (5 – 10 %) (141, 142).

The presence of other comorbidities was high in our study sample (67 %). The most reported comorbidity was thyroid disease (30 %), similar to what Tavakkoli et al. (59) found for NCGS females (27 %). An invitation letter to the study was however found to have been posted on the facebook page of the Thyroid Society of Norway, which may have resulted in a higher prevalence of thyroid patients in our population. Gluten is thought to worsen the hypothyroidism among thyroid patients (143), which could explain the motivation for someone to post this. This study found that a high proportion of NCGS patients with B₁₂ levels above normal (16 %) which could be due to supplement use. A reason for supplement use may be an earlier deficiency. B₁₂ status has not been investigated in NCGS patients, but low B₁₂ levels are common in hypothyroidism (144).

Autoimmune diseases are described in other NCGS populations (9.5 % and 7.5 %) (46, 81). In general, NCGS patients are found to have a lower prevalence of autoimmune disease than CD patients (37, 59, 81, 145), which appears reasonable since no autoimmune pathophysiology seems to exist.

Although the use of nutritional supplements was lower in our NCGS population compared to that of Biesiekierski et al. (46 % versus 60 %), the supplements used were similar. This

comparison held for cod-liver oil (27 % versus 28 %), D vitamin (20 % versus 28 %), multivitamins (18 % versus 25 %), B vitamins (9 % versus 10 %) and probiotics (7 % versus 8 %), respectively (68). These results are also comparable to the general Norwegian population (40 – 49 years) examined in Norkost 3, where 53 % used supplements and the proportion increased with age (88).

Almost half of our participants reported avoidance of other foodstuffs in addition to gluten. Of those with food avoidances 79 % eliminated dairy products from their diet (52 % of the total study sample), being the most common food items avoided. This is comparable to the results of Tavakkoli et al. (59). High frequencies of food avoidances have also been found in other studies (46, 68), and the exclusion of dairy products is common (68, 90, 146). Lactose intolerance may be present, but the prevalence seems to be variable (46, 59). Restricting foods high in FODMAPs other than lactose was also common in our NCGS patients (56 % (36 % of the total study sample)), although the FODMAP content of participants' diet was yet to be analysed. Similar to our finding, Biesiekierski et al. (68) found that 43 % of NCGS patients performed FODMAP restriction, and all participants fulfilled the criteria for IBS. In our study, 30 % of participants fulfilled the IBS standards, a similar prevalence as found in the NCGS population studied by Brottveit et al. (75), and comparable to the prevalence of IBS symptoms in treated CD patients (62, 75).

Overall, our study population seemed to have similar characteristics as those described by other authors. However, our NCGS sample had a higher prevalence of hypothyroidism and higher proportion had relatives with CD compared to other studies (39, 46). Prevalence of NCGS subjects disabled from working is not described elsewhere.

5.3 Nutritional status

5.3.1 Body mass index

Our study participants had an average BMI within the normal range (24.8 kg/m²). BMI for NCGS patients in other studies range from: overweight (81), to normal (24, 59), and even underweight (93). Overall NCGS patients seem to have BMI within normal range (24, 59). Whether shifting to a GFD results in changed BMI has not been investigated in NCGS subjects. Further, we do not know the body composition, or waist circumference – which could predict life-style.

The BMI found in our study sample suggests that a GFD is not a weight-loss diet, despite popular misconceptions that have lead people to go gluten-free in order to lose weight (147). On the contrary, a retrospective cohort study assessing the effect of a GFD on BMI in 679 CD patients found that the overall BMI increased on a GFD (148). At diagnosis CD patient had a lower BMI than the local healthy population, although 21 % was overweight and 12 % was obese. On a GFD diet, 16 % moved from normal or low BMI to overweight, and 22 % in the overweight group gained more weight. Weight gain was especially seen in those adhering strictly to the GFD (148). The GFD may increase risk of obesity by a combination of improved absorption, hypercaloric content of gluten-free foods and frequent snacking (149). This highlights the importance of monitoring and maintenance of weight as part of nutritional counselling in patients requiring a GFD (150).

5.3.2 Nutrient intake

Macronutrients

The energy proportion of total fat intake (43 E %), including saturated fat (14 E %), exceeded the upper limit of the recommended intake at the expense of carbohydrates intake which was lower than recommended (40 E %). These imbalances were also seen within the general Norwegian population (88). In Norkost 3, both female and male participants had a higher intake of saturated fat (13 E %) and lower intake of carbohydrates (43 – 44 E %) than recommended.

Few studies have been published on nutrient intake in NCGS populations. Only one available publication evaluating nutrient intake in 22 Italian NCGS patients, based on a 7-day food diary, has been found (151). These data are therefore used for comparison with our results. The Italian NCGS patients had an intake of macronutrients within the recommended range (151). This indicated that our NCGS patients had a less healthy diet quality than those in the Italian study. Treated CD patients are found to have a higher fat intake and a lower carbohydrate intake than healthy controls, in particular for females, but within the preferred ranges (152-154). Further, IBS patients are described to have a lower carbohydrate intake on a low-FODMAP diet compared to controls on a normal diet, although the carbohydrate intake was optional. The total fat intake of IBS patients were adequate (155). A high fat intake in replacement for carbohydrates was also seen in a Norwegian CD population evaluated by a master student of clinical nutrition, and it was argued that this could be explained by the low

carbohydrate diet (LCD) trend (156). As the LCD has currently faded in popularity it can be assumed that the high fat intake is a result of the GFD. However, some of our participants may still be adhering to the LCD, giving that the carbohydrate intake in the general Norwegian population is low. Utilization of egg, meat, seeds, nuts, butter and other fatty dairy products was high for some participants, replacing carbohydrate-rich alternatives and probably elevating the average fat intake.

A trend towards increased fat consumption after treatment with GFD in CD patients has been discovered recently (92). Miranda et al. (91) found that core gluten-free foods – gluten-free bread, pasta and dough/pastry/pizza products – contained significantly more fat, including saturated fat, than gluten-containing counterparts, consistent with a similar study from Canada (157). This gave a significantly higher percentage of energy from fat for those on a GFD, but only for the female participants (91). The fat content in gluten-free products can be explained by the utilization of fatty ingredients to optimize taste, palatability and texture in cereal alternatives, and might promote weight gain (158). Two recent studies found that gluten-free products showed similar nutrition qualities as regular foods, except regarding proteins (159, 160). However, low content of fibre and high content of saturated fats have been seen in the gluten-free products (159).

Another explanation of the higher fat intake may be a greater frequency of snacking on less-healthy foods. Snacking behaviour can be influenced by the low protein and fibre content in gluten-free products that reduce the feeling of satiety (161, 162). Even though our NCGS sample had a high intake of protein, occasional low availability of healthy gluten-free products and lack of planning could have contributed to unhealthy food choices. In addition, gluten-free foods do not always meet consumer preferences as regards consistency, taste and price (160, 163).

Intake of dietary fibre (19 g) was lower than the recommended intake and slightly lower compared to the average Norwegian population (88). The discrepancies are thought to be caused by the higher carbohydrate intake among participants in Norkost 3. In addition, the participants in Norkost 3 were found to have a higher educational level than the average population, giving reasons for intake of carbohydrates high in fibre, following a correlation between healthy choices and educational levels (88). On the other hand, NCGS patients had an equal intake of dietary fibre when compared to the Italian NCGS patients, despite unequal carbohydrate intakes (151). This suggests that the carbohydrate-containing food choices in

our NCGS patients were richer in fibre (e.g. oats) (89). A recent study performed by Shepherd et al. (92) found that the intake of dietary fibre was somewhat below recommendations in diet-experienced CD patients (22.0 g), but the intake was actually higher than in the healthy Australian population (20.3 g). This is different from earlier studies. A Swedish study from 2001 conducted by Grehn et al. (164) found that treated CD patients had significantly lower fibre intake than healthy controls and recommended intake. The female participants in this study had a mean intake of fibre of 11.5 g, whereas healthy controls ate 16 g fibre daily. Hence, this suggests that the fibre content of gluten-free food has increased together with a wider spectre of gluten-free food choices available. In general, there has been an increased focus on the health effects of adequate intake of dietary fibre.

In summary, NCGS patients showed an imbalance in intake of macronutrients. Total intake of fats, including saturated fats was higher and the intake of carbohydrates and fibre was lower than recommendations. NCGS patients seemed to have an unhealthier macronutrient-profile compared to other NCGS, CD and IBS patients, as well as to the average Norwegian population. As high fat intake might increase the risk of coronary heart disease, it would have been of interest to measure cholesterol and triglyceride levels in NCGS patients.

Micronutrients

Iron

Almost all (98 %) of the female study patients consumed less iron than recommended: average intake was about 50 % lower than recommended (8 mg) comparable to the intake of Norwegian females (88). This is a problem within the Norwegian population, with half of the population susceptible to under-consume iron (88). The iron intake of NCGS females was also similar to that of Italian NCGS patients (151), but lower than the intake of treated female CD patients (11.2 mg) and treated IBS patients (9 mg) (92, 155).

On the other hand, only 3.3 % of our NCGS sample exhibited iron deficiency, similar to the finding of other studies (81, 139). However, some iron deficiency has been reported in NCGS populations on a gluten-containing diet (in about 19 % and 15 %) (39, 165). Treated CD patients have been found to recover from iron deficiency when starting a GFD (166). In our NCGS sample, relief in symptoms on a GFD may increase appetite and further improve iron status. In addition the utilization of supplements containing iron may have improved iron status in NCGS patients, and may explain the low level of iron deficiency.

Folic acid

Intake of folic acid was lower than recommended in NCGS females (208 µg) but was comparable to Norwegian females. Too low intake of folic acid was also seen for NCGS males (209 µg). This deviated from the average male population in Norway, which consumed almost adequate amounts of folic acid. Low intake of folic acid can in general be explained by inadequate intake of carbohydrates in the form of grains, leafy vegetables and fruits. The Italian NCGS patients had an adequate intake of folic acid of 326 µg, indicating a higher intake of vegetables and fruits compared to our NCGS sample (151). Inadequate consumption of folic acid has been found in several studies evaluating diet history in CD patients (164, 167). Some of this may be explained by scarce folic acid content in gluten-free products composed mainly of refined flour; however fortification with B vitamins may have become more common in gluten-free products (89). Deficiency of folic acid was not seen in our NCGS study sample, and is rarely found in other NCGS populations (46, 165).

In a Swedish study (168), inadequate intake of B vitamins was associated with elevated homocysteine levels in the blood of treated CD patients. Supplementation with B vitamins, including folic acid, reduced homocysteine levels and improved general well-being, notably anxiety and depression moods. This could possibly be transferred to some NCGS patients as 3 % and 30 % had similar or lower values of folic acid and B₁₂ respectively as compared to the CD patients in the Swedish study before they got supplements.

Vitamin D

Intake of vitamin D was lower than recommended for NCGS females and males (6.7 µg and 5.8 µg, respectively). Since our analysis of dietary intake includes intakes of cod-liver oil, utilized by 27 % of participants, we have compared vitamin D intakes with those of Norwegian females and males after inclusion of supplements in Norkost 3 (10 µg and 12 µg); these were adequate and higher than in NCGS females and males. Low intakes of vitamin D both in our NCGS subjects and the general Norwegian population, can be caused by weak sun in the winter months (169, 170), with few vitamin D rich dietary sources available, apart from fatty fish (171). Though, consumption of fatty fish is in general lower than recommended in the Norwegian population (88). Interestingly, the Italian NCGS patients had an extremely low vitamin D intake of 2.2 µg with high risk of deficiency (151). Consumption of fish (and cod-

liver oil) is more likely among Norwegian NCGS patients, perhaps also compared to other foreign NCGS populations, as a result of more readily available sources of fatty fish (170).

None of NCGS patients were found to have vitamin deficiency (< 25 nmol/L), but 9.5 % had suboptimal intake of vitamin D (< 50 nmol/L). Further calculations showed that 63.5 % had serum levels below the ideal value of 75 nmol/L, proposed for further improved health (117, 172). Volta et al. (46) found that 11 % of the NCGS patients were vitamin D deficient, but no reference value was given. Unfavourable vitamin D levels in NCGS subjects have also been described by other authors, where 15 % had non-optimal levels between 25 nmol/L and 75 nmol/L (139). The proportion of patients with vitamin D levels below 50 nmol/L was not described in this study by Kabbani et al. (139). An international standardization project (Vitamin D Standardization Programme, VDSP) has been established with the aim of standardizing 25-OH vitamin D in serum (172).

A possible consequence of vitamin D deficiency in NCGS patients could be gastrointestinal symptoms. A recent study of the role of vitamin D in IBS has found that correction of vitamin D deficiency (< 50 nmol/l) resulted in reduced gastrointestinal symptoms, followed by improved quality of life (173). This might be explained by the anti-inflammatory effect of vitamin D in the gut (174). Hence, these patients may benefit from higher vitamin D levels, closer to 75 nmol/L (173). As 35 % of NCGS patients were found to have low grade inflammation in the intestine, they could possibly have benefit of more vitamin D.

Calcium

Intake of calcium was lower than recommended intake for females (694 mg) and males (579 mg). NCGS patients had a calcium intake below that of the general Norwegian population, in particular for the males (579 mg versus 1038 mg). The average calcium intake of the NCGS sample was similar to the Italian NCGS patients. The low calcium intake is probably associated to the exclusion of dairy products. Low intakes of calcium are also reported in IBS patients due to reduction of high-FODMAP foods in their diet, such as minimising the intake of dairy products, without compensating using lactose-free dairy alternatives (155). Data on lactose intolerance in NCGS are variable, but prevalence of about 35 % is suggested (46, 59). Lactose intolerance is found to be present in about 50 % of IBS patients (175, 176). Non-optional calcium intakes are also seen in treated CD patients (92), even if many will recover from lactose intolerance after adhering to the GFD (177).

It is concerning that many individuals may falsely self-diagnose themselves as lactose intolerant (178). In general up to 12 g of lactose (240 ml of milk) in one meal can be tolerated in most patients with true lactose intolerance. Further, yoghurt and other fermented dairy products (like kefir) should be tolerated better due to content of lactic acid bacteria; and hard white cheeses are without lactose (179). This means that dairy restrictions are stricter than required and that an adequate intake of calcium could be achieved, also in lactose-intolerant patients.

Acute symptoms of calcium deficiency are very rare, as the mineral deposition in the bone keeps the calcium level in the blood adequate at all time. Chronic insufficient supply will reduce bone mineral density and increase risk of osteoporosis, especially in combination with suboptimal vitamin D status and inactivity (179).

Iodine

Intake of iodine met only half of the recommended intake for females (76 µg) and less than half for males (62 µg). Iodine intake was not measured in Norkost 3, but the National Council of Nutrition has estimated iodine intake in the general Norwegian population based on data from Norkost 3 (180). These estimates showed that the intake of iodine was 110 µg and 145 µg for females and males respectively: hence our NCGS sample had a much higher risk of iodine deficiency (181). Few sources of iodine are available in the Norwegian diet, iodine mainly stems from dairy products and fish. Dairy products is of the most important dietary source of iodine in the Norwegian diet (180).

Iodine status in a population is determined by measures of iodine in multiple urine samples. Another and more easily method is to evaluate the intake of iodine. Iodine status by urine samples was not measured in our NCGS participants. Iodine is essential for the production of thyroid hormones (triiodothyronine and thyroxine) that regulate the body's metabolism. If the iodine intake is inadequate the production of these hormones will be reduced. There is an increased risk of developing fatigue and hypothyroidism from seriously low iodine intake in our NCGS patients (179).

In summary, consumption of essential micronutrients was lower than recommended as regards iodine, calcium, iron (for females), vitamin D and folic acid. Micronutrient deficiencies were hardly seen, though iodine deficiency might be present. This could be explained by the use of supplements and meal replacements and from varying intake of

micronutrients over time. NCGS patients had lower intakes of iodine, calcium and D vitamin, than the average Norwegian population. Regarding iodine, the Norwegian Council of Nutrition has recently affirmed that the iodine intake in Norway is concerning low, and that an intervention to increase the intake of iodine is warranted. Differences between our NCGS patients and the Italian NCGS patients may be due to unequal country-specific dietary habits. Compared to diet experienced CD females in the study by Shepherd et al., our NCGS patients had much lower intakes of calcium, iron and folic acid (vitamin D and iodine were not measured in this study).

5.3.3 Gluten-free diet adherence

Eighty-two percent of participants reported to be totally gluten-free throughout the past six months, whereas 19 % reported to adhere to the GFD most of this time. Hence, gluten induced symptoms may be more frequently presented in the latter group. The adherence questionnaires and food diaries showed very good compliance to the GFD, even though 60 % of participants were self-educated, and only 5 % had received instruction from a dietician. Gluten avoidance without seeking medical advice is common in NCGS patients (59, 68). Perhaps readily available Internet information and exposure to gluten-free products via blogs and gluten-free groups provide valuable experience-based information (182). Additionally, the expansion of the gluten-free market in Norway together with better labelling of gluten-free products makes it easier to avoid gluten-containing foods (183). A Norwegian study of GFD adherence in NCGS patients and CD patients found NCGS patients to have equally good adherence as the CD patients, even though a significantly higher proportion of the NCGS patients (91 %) compared to the CD patients (9 %) were self-educated in the GFD (90). Excellent GFD adherence was also found in another NCGS population evaluated by Biesiekierski et al. (68), where 44 % of the participants were self-educated in the gluten-free diet, without dietetic supervision. Still, it is not certain that the studied NCGS populations are representative for all NCGS populations.

5.4 Clinical symptoms

The aim of this study was not to evaluate the origin of symptoms but to evaluate their presence on a GFD. HRQoL was used to evaluate the burden of NCGS as compared to normative data. The findings of symptoms are mainly compared to results from the study by

Brottveit and colleagues (75), due to comparable demographic between the NCGS populations, and the use of similar symptom questionnaires.

5.4.1 Gastrointestinal symptoms

In general patients with self-reported NCGS report improvement in gastrointestinal symptoms on a GFD, and only such patients were qualified for participation in this study. A cut-off for uncontrolled symptoms, in concordance with IBS, has not been established in the use of GSRS-IBS. Therefore, the result from GSRS-IBS is difficult to interpret and few studies are available for comparison. Gastrointestinal symptoms measured by VAS were all close to or lower than 10 mm, which indicates symptom control as described by Carroccio et al. (71). On the other hand, it seems likely that a substantial proportion of NCGS patients had persistence of gastrointestinal symptoms after gluten withdrawal: About one third reported symptoms in concordance with Rome III criteria. These patients had a significantly higher GSRS-IBS score ($p=0.003$) than those not having such symptom behaviour. Therefore, inclusion of patients that still experienced symptoms may have occurred.

Several studies describe persistence of symptoms after gluten withdrawal: Biesiekierski et al. (68) found that 22 % of NCGS patients reported to have uncontrolled symptoms, and Tavakkoli et al. (59) found that a majority of NCGS patients complained of bloating, abdominal pain and diarrhoea on a GFD. Further, Brottveit and colleagues (75) found, using the GBB for gastrointestinal symptoms (124), that NCGS patients reported more gastrointestinal symptoms than CD patients, and that both patient groups experienced more symptoms than healthy controls. In both patients groups, about one third had symptoms in line with Rome III criteria, similar to our NCGS patients (75). When considering Figure 2 in the study by Brottveit et al. (75), NCGS and CD patients seem to have almost equal scores for GSRS-IBS. These scores appeared to be lower than the GSRS-IBS score of our NCGS patients, suggesting more severe gastrointestinal symptoms in our study.

As mentioned in the introduction, non-adherence can probably explain a large part of symptoms in CD patients, possibly also in NCGS patients. In cases of uncontrolled symptoms, intake of foods high in FODMAPs may also cause persistence of symptoms on a GFD (184, 185).

5.4.2 Fatigue and tiredness

Our NCGS patients were found to be suffering from fatigue and tiredness. Fatigue also affected the NCGS patients in the study by Brottveit et al. (75), where symptoms of fatigue were comparable to CD patients, but higher when compared to healthy controls. Our NCGS patients were found to be more severely affected by fatigue as our median results from GBB-exhaustion was higher than the corresponding mean results in NCGS patients investigated by Brottveit and colleagues (75). Fatigue is a commonly reported symptom in NCGS patients. Tavakkoli et al. (59) found that fatigue was the third most common symptom after bloating and abdominal pain in NCGS patients on a GFD, with a prevalence of 50 %. Further, in concordance with our results, Volta et al. (46) found tiredness to be the most frequently reported extra-intestinal symptom.

In the first randomized controlled trial with suspected NCGS patients, performed by Biesiekierski et al. (24), fatigue was reduced following gluten withdrawal. Biesiekierski later reformulated the hypothesis that gluten could cause fatigue, when reduction in FODMAP-containing foods was found to be a more likely explanation for improvement in fatigue (25). Fatigue may indirectly be explained by FODMAPs, due to relief in symptoms and change in the gut microbiome (186, 187). The mechanisms of gluten on fatigue are not defined, but it has been hypothesized that gluten can cross the gut epithelium (leaky-gut syndrome) and pass the blood-brain barrier acting like a neuropeptide, potentially causing extra-intestinal symptoms (188).

The presence of fatigue in CD patients has also been reported (189), and may persist even after treatment with a GFD (15, 189). Fatigue could be due to non-adherence and iron deficiency anemia (190). Further, reduced quality of sleep is also common in CD patients, and could explain the more severe fatigue (191). Given the overlap between NCGS, IBS and food hypersensitivities, IBS patients and patients with food hypersensitivities are also found to suffer from fatigue (127, 192, 193). However, unlike NCGS patients (75), fatigue reported by IBS patients is thought to be more due to psychological distress in addition to symptom severity (192, 193). In our NCGS patients it is likely that the relative high presence of hypothyroidism and other medical conditions could have exacerbated the average fatigue scores (194).

5.4.3 Depression

One fifth of our NCGS sample was classified as having mild depression. When compared to the prevalence of depression measured by BDI-II in the general Norwegian population (females and males), twice as many in our study were found to have mild depression. Moderate depression was actually higher in the average Norwegian population, while the prevalence of severe depression did not differ (130)³. Volta et al. (46) found the prevalence of depression to be 18 % for their NCGS patients.

Our results differed from those of Brottveit et al. (75), who found no symptoms of anxiety and depression – neither in NCGS subjects nor in CD patients, similar to healthy controls. In this study anxiety and depression were measured by Hospital Anxiety and Depression Scale, developed for screening of depression in hospital outpatient clinic (195), possibly explaining the diverging results.

A clinical trial has recently demonstrated that gluten could cause depression in NCGS patients after only three days with gluten challenge (105). The diet was low in FODMAPs, which indicates that gluten ingestion may be related to symptoms of depression (105, 196). Another explanation for depressive symptoms in our study could be the presence of symptoms from the gut (76): When symptoms from the gut exist, depression may co-exist. The presence of depression in treated CD patients might be related to how a GFD brings limitations to daily life and social activities with few strategies for handling the diet, in particular within CD females (197). In addition, sleep disturbances may also be responsible for symptoms of depression in CD patients (191). All these factors may be transferable to NCGS patients. Furthermore, being in an undiagnosed state could influence mental health.

5.4.4 Subjective health complaints

The prevalence of subjective health complaints was higher among NCGS participant for gastrointestinal pain, pseudoneurological complaints, allergy and musculoskeletal pain, and less for flu, when compared to the general Norwegian female population (132)⁴. These results indicated that the total burden of subjective health complaints was high in the NCGS

³ Prevalence of depression measured by BDI-II in the general Norwegian population, ≥ 18 years: Mild depression; 10.6 %, moderate depression; 6.0 %, severe depression; 2.4 %.

⁴ Prevalence of any subjective complaints among Norwegian females, ≥ 15 years (score above 0): Musculoskeletal pain; 84 %, complaints related to pseudoneurology; 71 %, gastrointestinal pain; 61.8 %, flu; 55 %, allergy; 37 %.

participants and therefore might impact their work situation. Gastrointestinal symptoms together with tiredness and muscle/joint pain have been found to co-exist in suspected NCGS participants (46), in line with results of this study (Figure 7). The overall reported intensity of health complaints seemed low among our NCGS study patients. The intensity of the subscales in the SHC inventory showed that participants had close to similar health complaints as compared to the general Norwegian female population in regards to musculoskeletal pain, gastrointestinal pain and pseudoneurology (132); however allergy and flu were considered less bothersome in NCGS patients (132)⁵. Musculoskeletal pain together with gastrointestinal symptoms has been found in patients with food hypersensitivity as well, where the symptoms are suggested to be food-induced (127). The subscale pseudoneurology included tiredness, sleep problems, anxiety and depression. These health complaints, together with gastrointestinal pain, support the findings of the aforementioned presence of fatigue and gastrointestinal symptoms as measured by GBB and GSRS-IBS.

5.5 Health-related quality of life

NCGS patients reported lower general health, vitality (energy/fatigue), bodily pain, physical functioning and to some degree lower mental health than the general Norwegian female population (137)⁶. This suggests that the load of symptoms NCGS patients experience reduces their quality of life, especially fatigue, affecting their well-being. The low score for bodily pain (reduced health perception) may correspond to symptoms from the gut. Bodily pain may also refer to musculoskeletal symptoms which are highly related to fatigue (98, 127).

As regards to the study by Brottveit et al. (75), similarities were seen for general health and bodily pain, with significantly lower quality of life than among healthy controls. The scales for vitality and mental health were not different from healthy controls in the study by Brottveit and colleagues (75), differing from our results. They (75) also found low physical and social functioning, whereas our participants had higher scores than the general Norwegian population for these scales (137). The CD patients in this study were only found to have reduced score for vitality (75). Although HRQoL was reduced for some aspects, NCGS

⁵ Intensity of complaints in Norwegian females: musculoskeletal pain; 5.5, pseudoneurology; 3.78, gastrointestinal pain; 3.5, allergy; 2.6, flu; 2.4.

⁶ Mean SF-36 scale scores for Norwegian females 40-49 years: Physical functioning; 89, role physical; 83, role emotional; 84, bodily pain; 74, social functioning; 86, mental health; 78, vitality; 59, general health; 79.

patients` perceived health seemed to improve the last year. This suggests a positive change resulting from gluten withdrawal, as shown by the high score on the health transition item.

Improvement of HRQoL is found in CD patients following a GFD (198). CD patients are found to believe they have the same HRQoL as healthy individuals (199), although reduced HRQoL exists, especially among females (200). Fatigue is also associated with impaired HRQoL in CD patients (190). In IBS patients gastrointestinal symptoms as well as fatigue and impaired mental health are known to reduce HRQoL (201). In general, chronic gastrointestinal symptoms are associated with reduced quality of life (122). This increases the likelihood for reduced HRQoL in our NCGS patients.

In summary, both gastrointestinal symptoms and extra-intestinal symptoms (fatigue and mild depression) were present on a GFD. HRQoL was reduced compared to normative data, especially for general health and vitality. NCGS patients seemed to have more symptoms regarding gastrointestinal symptoms, fatigue and depression as compared to NCGS patients studied by Brottveit and colleagues.

5.6 Strengths and limitations of the methods

5.6.1 Study design

An advantage of this cross-sectional study is that it allowed us to investigate many variables, which provided valuable insight in health related characteristics of NCGS patients.

Furthermore, this design can indicate associations and is valuable in generation of issues and hypothesis for future research (202). This is valuable since NCGS is still not fully understood.

On the other hand, a cross-sectional study could not provide any valid conclusions about cause and effect. Further, this study did not have a matched control group which would have been useful when interpreting the data. The consecutively noting of dietary intake reduces chance of memory bias which strengthens our data. In addition, the response rate was high regarding the questionnaires which reduced the likelihood for misclassification, which is often a problem in the methods linked to cross-sectional studies. One disadvantage with this study is that it was prone to unmeasured confounding factors: The high prevalence of hypothyroidism may have had impact on our findings: energy intake could have been higher, and symptom burden may actually have been lower. Therefore, the results should be interpreted with caution. Also other additional diseases and medications may have influenced

our results. Thirdly, dietary intake of FODMAPs needs to be assessed. This could also have been a confounding factor. Additionally, other food intolerances could have generated symptoms.

5.6.2 Study sample and recruitment

A main strength of this study is that NCGS patients seemed to be highly motivated participants, as it may provide further insight into symptom triggers. This may have had beneficial impact on the completion of food diaries which demanded a substantial effort on the part of the NCGS patients. In addition, the good adherence to the GFD increases the validity of the dietary results and symptoms which were meant to describe the NCGS patients on a GFD. Additionally, the response rate was very high among participants, partly because all baseline questionnaires were cross-checked after completion.

However, the moderate sample size selected in close proximity to Oslo reduces the representativeness of our sample. Also, the voluntary participation and possibility for financial support from the Norwegian Labour and Welfare Administration for the extra costs of gluten-free products as an outcome after DBPC-gluten challenge may have attracted NCGS patients with a higher symptom burden, causing possibilities for selection bias.

5.6.3 Validation of the dietary assessment

One may assume that underreporting occurred in the study sample, as discrepancy between the expected and estimated PAL (EI:BMR) was seen. According to an expert report from FAO/UNU/WHO from 2001 the mid-point PAL for being mostly sedentary doing light activity is set to 1.55 (1.4–1.69) (86), which is the yardstick in Goldberg's equation (115, 138). It is suggested that this activity level was too high for NCGS patients, in view of the presence of fatigue and comorbidities (hypothyroidism, migraine, fibromyalgia, ME) hence the cut-off could actually have been set lower, but this is difficult when only having subjective measures on the activity level. Another way of estimating underreporting is by calculating deviance by 20 % of reference intake as described by Mela and Aaron (203), also used by Shepherd et al. (92). This method suggests that reported intake did not differ considerably from actual intake (results not shown).

5.6.4 Food diary

Utilization of a 7-day food diary is considered as the best-practice for measuring the dietary history of adults when the aim is to compare the intake of energy and nutrients with recommendations (204). Dietary intakes were acceptable as household measures and weighted values. This may have increased accuracy of the data. By interpreting data by household measures, less effort from participants could be expected and could give good estimates on nutrient intake. With food diaries, omission or addition of food items may occur, as behavioural changes have been reported to occur when registering diet history (203, 205). In the case of recording a GFD with its restriction in the variation of food choices, it is reasonable to assume that only minor changes in food habits have occurred during baseline. Further, many participants reported having a diet with minimal variation. As an individual's dietary intake may vary with the seasons, a 7-day record period may be inadequate for measuring these fluctuations. Such variation is minimized in this study since the food diaries have been collected at variable time during a period of more than one year. Adequate information on how to register the food consumed by participants is crucial for validity of the food record. Face-to face training in how to record the diet was performed and strengthens the method: however not all participants registered the amounts of food eaten, only what kind of food they ate. In such cases our estimates of amounts of food eaten were based on similar dishes, with possibilities for divergences. Not all participants provided recipes for homemade dishes, or recorded food labels on commercial gluten-free products. This may have resulted in inaccurate calculations in some cases. Most food diaries were registered in the *Diet Planner* by the author of this thesis. However, as two other dietitians (Ingunn Hillestad and Gry Skodje) also assisted, variation in methods of registration cannot be ruled out. These considerations may reduce the reliability of the nutrient intakes which should be interpreted with caution.

Calculating nutrient intake

The Diet Planner utilized to analyse the nutrient content of the food diaries is an updated version of the earlier programme 'Mat på Data', and was launched the autumn 2014. *The Diet Planner* contains many foods used in a habitual diet, but the programme lacks nutrient information on gluten-free foods. Many of the gluten-free foods entered in *the Diet Planner* had detailed information on macronutrients, including fibre, but micronutrients were poorly described. This reduces the reliability of micronutrient intake of NCGS patients. To give as

good estimate of micronutrient intake as possible the gluten-free breads and cracker bread within *'the Diet Planner'* were used for all different types consumed. This strengthens the reliability of micronutrient intakes, since breads are the main gluten-source in the Norwegian diet (88).

Overall, the data on intake of nutrients is most reliable for macronutrients presented as energy proportion of the total intake, as one can expect minor differences if the energy intake actually were higher. In addition, the intake of micronutrients can vary considerable from day-to-day, and data for this is most valuable for food frequently eaten, e.g calcium because of habitual milk consumption (204).

Comparison with Norkost 3

Comparing results against the general Norwegian population is a strength when interpreting data and evaluating group specific abnormalities. When comparing the nutrient intake in the NCGS sample to the intakes in Norkost 3, several factors must be considered. First of all, two different methods have been used for assessing dietary history, a 7-day food diary in our study as against 24-hours recall interviews in Norkost 3 (88). The 24-hours recall method for assessment of food history is a retrospective method performed by an interviewer, entailing memory bias and the likelihood of interview errors and it is more prone to day-to-day variations of the nutrient intake. Additionally, 24-hour recall was obtained for only two days in Norkost 3, which is arguably not enough to enable comparison with our study group. Although, different methods were used, the number of participants in Norkost 3 gives possibility for good estimates on food intake. Secondly, the participants in Norkost 3 were found to have a higher educational level than the average Norwegian, increasing chance for a healthier lifestyle. Thirdly, the participation percentage was very low in Norkost 3 (37 %). This reduces the representativeness of the data. Minor differences between our NCGS sample and the general Norwegian population may exist; the carbohydrate intakes may be higher, and micronutrient intakes may be lower in the other general Norwegian population.

Comparison of our study group to Norkost 3 is most valuable for the females, given the low number of male participants. Comparisons between the NCGS males and males in Norkost 3 must be interpreted with caution. The skewed distribution of females and males can also explain why we did not see many differences in nutrient intakes between females and males, as was found in Norkost 3, giving the chance for type II error where true differences not were

found. However, minor differences may be expected as our study group was a more homogenous group, given the restrictive nature of the GFD.

5.6.5 Gluten-free diet adherence

The adherence questionnaire used in this study was developed for the purpose of this study. The original adherence questionnaire was developed specifically to measure adherence in Norwegian CD patients and was found to have good specificity (118). However, the specificity and reliability was not tested specifically on the excerpted adherence questionnaire, and may therefore possess some reduced specificity, and reliability was not investigated. In addition, the quality of the knowledge test was not tested. This could reduce the accuracy of the results from these questionnaires. Anyway, there is a lack of standardized methods to assess GFD adherence. In the study by Nilsen (118), different adherence tools was found to be inconsistent in measuring compliance to GFD. Moreover, the gold standard for assessing adherence is made by an expert dietitian evaluation (119). As, this study assessed adherence by three different methods; a questionnaire, a knowledge test and through evaluation of dietary intake, the result is suggested to be reliable.

5.6.6 Methods for assessment of clinical symptoms and HRQoL

Baseline interview

The baseline interview was guided by a CRF standardizing the information collected. As the interview was performed by four different people; Gry Skodje, Christine Henriksen, Ingunn Hillestad and the author of this thesis, some variation may still exist.

Questionnaires

A major strength of this study was that clinical symptoms were measured by four different instruments: GSRS-IBS, GBB, BDI-II, SHC and SF-36. These questionnaires applied together gave information of a wide spectre of symptoms, not only physical symptoms and complaints but also psychological disturbances. Further, the measuring of HRQoL by SF-36 provided high quality information of disease burden. An advantage with the questionnaires used in this thesis was that all have been evaluated as being reliable and valid. In addition, the questionnaires were user-friendly and easy to complete, with the possible exception of SF-36.

Further, the questionnaires, GSRS-IBS, GBB, SHC and SF-36 have been recently used on a Norwegian NCGS study population, enabling comparisons (75). One limitation for all questionnaires was the modification made to reflect the past week. This might affect the accuracy of results, as seven days may not be sufficient to monitor the patients` normal situation. Especially as regards SHC and SF-36, originally meant to reflect the last month, these results should be interpreted carefully. The specific advantages and disadvantages of the questionnaires` are described below.

Gastrointestinal Rating Scale-IBS

As the gastrointestinal symptoms overlap in IBS, CD and NCGS patients (22), the Gastrointestinal GSRS-IBS was deemed well-suited for detecting gastrointestinal symptoms in our NCGS sample. Further, a modified version, also including extra-intestinal symptoms, is suggested as part of the diagnosis of NCGS proposed by an expert group (8). An advantage of GSRS-IBS is that the questionnaire has been shown to have good psychometric properties, where the dimension scores correlate with quality-of-life instruments as well as an anxiety and depression inventory (122). This strengthens the possibility for an association between gastrointestinal symptoms and reduced HRQoL and symptoms of depression found in our study sample. It can be argued that one week is too short a time for measuring gastrointestinal symptoms, as IBS symptoms are known to vary considerably over time (206). However, substantial variations in symptoms from the gut are less likely to occur in NCGS subjects on a GFD, given that our sample consists of true NCGS patients. Complementary to GSRS-IBS, gastrointestinal symptoms by a visual analogue scale were measured due to the frequent use in other studies on suspected NCGS populations (24, 25, 71).

Giessen Subjective Complaint List

GBB was used to evaluate symptoms of fatigue in NCGS patients. Although, GBB is not validated in Norway an experienced psychiatrist at OUH recommended utilization of this questionnaire due to its ability to measure fatigue in patients who do not have a disease involving chronic fatigue, like ME. Alternatively, we could have used the Fatigue Impact Scale (FIS), which is validated and translated into Norwegian and widely used in relevant conditions including, NCGS, CD, IBS and food hypersensitivity (25, 190, 207). That questionnaire has also shown to have high internal consistency and good correlation with quality of life tools and subjective health complaints (SHC) (207).

Beck Depression Inventory-II

As BDI-II is used worldwide for self-assessment of depression and can evaluate symptom of depression in non-depressed as well as depressed patients, it was well suited for our study sample (130). BDI-II has been translated into Norwegian and it has shown to have solid psychometric properties. One limitation of BDI-II is that it is less suitable for distinguishing between individuals with transient psychological stress symptoms and those with chronic depression (130). This may reduce the accuracy of reported depression in NCGS patients.

Subjective Health Complaints

The subjective health complaints questionnaire (SHC) has been developed in Norway, and scores from the general Norwegian population have been collected (132). SHC is used widely at OUH Rikshospitalet when evaluating symptom burden in NCGS and CD.

Short Form-36

The Short-Form 36 is a generic questionnaire for measuring HRQoL suitable for use with any age, disease or treatment group. Further, the survey has been validated in Norway and translated to Norwegian, where it is broadly used. These properties of SF-36 were valuable in the current study as comparisons with the general Norwegian population could be made.

6 Conclusions

The main aim of this study was to describe nutritional status, symptoms and health-related quality of life in self-reported NCGS patients in their normal situation adhering to a GFD. The conclusions that can be drawn from the specific aims are summarized below.

Nutritional status

Overall NCGS participants were found to have good nutritional status. BMI was within normal range and nutritional biomarkers were within reference ranges. However, unfavourable high intake of fat and saturated fat was seen; whilst intakes of carbohydrates and dietary fibre were lower than recommended. For the micronutrients, suboptimal intake was seen for calcium, iodine, iron (females), and D vitamin, implicating that that NCGS patients on a GFD may be at risk of nutrient deficiencies. Iodine status is of special concern. Unnecessary dietary restriction was common. Moreover, NCGS patients reported excellent adherence to the GFD.

Clinical symptoms and health-related quality of life

Gastrointestinal symptoms persisted in some participants after self-treatment with GFD. NCGS patients also suffered from fatigue/tiredness and from mild depression. These symptoms seemed to be more pronounced than gastrointestinal symptoms. Even though HRQoL was reduced for some aspects, in particular fatigue and loss of energy, participants seemed to perceive their health to change towards the better after adapting to a GFD.

7 Future perspectives

The results of this study confirm that self-reported NCGS patients adhering to a strict GFD have an imbalanced intake of nutrient. This emphasizes the importance of nutritional supervision. Although the method for assessing nutrient intake was good, the tool for calculating nutrient intake may be inadequate, therefore it can be questioned whether these values are the true intakes of the NCGS patients studied. Future studies should focus on nutritional status in NCGS patients; in particular cholesterol levels and iodine status are of interest.

The burden of symptoms that may reduce patients` HRQoL should be taken seriously by healthcare professionals. These patients are having complaints that possibly could affect the ability to work, having an impact on social costs. In addition, a GFD can be an economic burden for the patients when the period from self-assessed NCGS to conformed diagnosis may be of long duration. There is a need for future studies to identify a diagnostic biomarker, to optimize treatment and to reduce the drain on healthcare time and resources.

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Appendices

Appendix 1: Consent form

Samtykke til deltakelse i studien

”Gluten- og FODMAP-provokasjon av ikke-cøliakisk glutensensitivitet”

Del av: «Glutenprovokasjon ved cøliaki og glutensensitivitet uten cøliaki»

Jeg er villig til å delta i studien Gluten- og FODMAP-provokasjon ved glutensensitivitet uten cøliaki

(Signert av prosjektdeltaker, dato)

Stedfortredende samtykke når berettiget, enten i tillegg til personen selv eller istedenfor

(Signert av nærstående, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Appendix 2: Study invitation



Invitasjon til deltakelse i forskningsprosjekt på Rikshospitalet ”Gluten- og FODMAP-provokasjon ved ikke-cøliakisk glutensensitivitet”

Del av ”Glutenprovokasjon ved cøliaki og glutensensitivitet uten cøliaki”

Voksne personer med mistenkt ikke-cøliakisk glutensensitivitet (ICGS) som har spist glutenfri kost i mer enn 6 måneder inviteres til å delta i et forskningsprosjekt på Rikshospitalet. Cøliaki må være utelukket, og man må oppleve bedring av sine plager på glutenfri kost.

Prosjektet har som mål å øke kunnskapen om ICGS. Dette er en diagnose uten god sykdomsforklaring. Det er kun spesialister som får stille diagnosen, og typen utredningen kan variere noe mellom sykehusene. Mange har av denne grunn opplevd ikke å få god utredning og oppfølging av sin glutensensitivitet.

I denne studien skal vi undersøke hvilken betydning gluten og kortkjedete karbohydrater (FODMAP⁷) i kostholdet har for plager hos disse personene. Målet er også å forbedre utredning og behandling av personer der vi mistenker ICGS. Konkret blir deltakerne bedt om å spise en müslibar med kjent mengde gluten, FODMAP eller placebo (ingen tilsetning) i til sammen tre uker. Deltagelse innebærer til sammen 6 besøk på Rikshospitalet i løpet av en 2 måneders periode. Med deltakelse vil du:

1. Få en grundig utredning av din glutensensitivitet:
 - a. Klinisk undersøkelse hos lege og gjennomgang hos klinisk ernæringsfysiolog
 - b. Gastroskopi, blodprøver og avføringsprøver
 - c. Utfylling av spørreskjemaer
2. Bli bedt om å spise en müslibar med kjent mengde gluten, FODMAP eller placebo hver for seg i totalt 3 uker
3. Bidra til at man kan få en bedre forståelse av sykdomsmekanismene ved glutensensitivitet uten cøliaki og en bedre utredningsmetode og behandling av tilstanden.

Studien er godkjent hos Regionaletisk forskningskomité. Ta kontakt dersom du ønsker mer informasjon og er interessert i å delta.

Med vennlig hilsen

Overlege ved Gastro undersøkelse ved Rikshospitalet, prosjektleder

Knut E. A. Lundin e-post knut.lundin@medisin.uio.no tlf: 23 07 24 00

⁷ FODMAP=Fermentable Oligo-, Di-, Monosaccharides And Polyols

Appendix 3: Clinical Report Form

**” Glutenprovokasjon ved cøliaki og glutensensitivitet” - Delprosjekt
Glutenprovokasjon ved ikke-cøliakisk glutensensitivitet**

Clinical report form

**Gry Irene Skodje
2014**

DELTAKER IDENTIFIKASJON (ikke navn):

OPPMØTE 2 DAG -7: BASELINE DATO: _____

Navn på fastlege: _____

Navn på legesenter: _____

Er det utført gastroskopi i forbindelse med cøliakiutredning? Ja / Nei
 Hvis Ja, spiste deltakeren gluten før gastroskopi? Ja / Nei

Dato: _____

Sted: _____

Utført gastroskopi ved annet sykehus: Innhente dokumentasjon og legge ved i CRF!

FAMILIE/ARV

Familiemedlemmer med kjent cøliaki? Ja / Nei

I så fall hvem? _____

Familiemedlemmer med ikke-cøliakisk glutensensitivitet Ja / Nei

I så fall hvem? _____

TIDA FØR OPPSTART MED GLUTENFRI DIETT

Var du plaget med mye trøtthet?	Ja / Nei / Ukjent
Hadde du jernmangel?	Ja / Nei / Ukjent
Hadde du folatmangel (B9)?	Ja / Nei / Ukjent
Hadde du D-vitamin mangel?	Ja / Nei / Ukjent
Hadde du magesmerter?	Ja / Nei / Ukjent
Hadde du diaré	Ja / Nei / Ukjent
Hadde du forstoppelse?	Ja / Nei / Ukjent
Hadde du luftplager?	Ja / Nei / Ukjent
Hadde du positiv blodprøve for cøliaki	Ja / Nei / Ukjent

Eventuelt detaljer i fritekst

ROMA III KRITERIER **FØR** OPPSTART MED GLUTENFRI DIETT

Har deltakeren blitt utredet for IBS?	Ja / Nei
Hvis ja, når?	
Irritabel tarm syndrom: Diagnosekriterier*	
Har du hatt tilbakevendende magesmerter/ubehag** i mer enn seks måneder?	Ja / Nei
Har plagene vært til stede i minst 3 dager per måned de siste 3 månedene?	Ja / Nei
Dersom Ja på minst ett av spørsmålene:	
To av følgende forhold må også være tilstede:	
1. Forsvant magesmertene/ubehaget** når du hadde vært på do?	Ja / Nei
2. Opplevde du forandring i avførings frekvens ved symptomdebut?	Ja / Nei
3. Opplevde du forandring i avføringens konsistens ved symptomdebut?	Ja / Nei
*Kriteriene gjelder for de siste 3 måneder med oppstart av symptomer 6 måneder tidligere.	
**Med ubehag menes følelse som ikke beskrives som smerte.	

OPPSTART AV GLUTENFRI DIETT

Varighet av glutenfri diett _____

Eventuelt tidspunkt for oppstart av GFD: _____ (dag) _____ (måned) _____ (år)

Har du kjent matvareallergi eller matvareintoleranse? Ja / Nei

Allergi matvare	Symptomer

Er det annet enn gluten som utelukkes fra kosten? Ja / Nei

I tilfelle hva? (Meieriprodukter, gjær, løk, etc)

Hvor har du fått informasjon om glutenfri diett? (Sett kryss)

1 Klinisk ernæringsfysiolog	2 Lege	3 Familie	4 Venner	5 Internett	6 TV	7 Aviser	8 Bøker

Andre kilder med spesifikasjon

Fylle ut kunnskapstest og etterlevelse av GFK **HER**.

Fylt ut spørreskjemaer:		Score
Kunnskapstest gluten utført?	Ja / Nei	
Martine-intervju utført? (Etterlevelse glutenfri kost)	Ja / Nei	

Kontrollere Martine-intervju/skjema og etterlevelse av GFK

Ja / Nei

TIDA ETTER OPPSTART MED GLUTENFRI DIETT

Var du plaget med mye trøtthet?	Ja / Nei / Ukjent
Har du hatt jernmangel?	Ja / Nei / Ukjent
Har du hatt folatmangel (B9)?	Ja / Nei / Ukjent
Har du hatt D-vitamin mangel?	Ja / Nei / Ukjent
Har du hatt magesmerter?	Ja / Nei / Ukjent
Har du hatt diaré	Ja / Nei / Ukjent
Har du hatt forstoppelse?	Ja / Nei / Ukjent
Har du hatt luftplager?	Ja / Nei / Ukjent

Eventuelt detaljer i fritekst

ROMA III KRITERIER **ETTER** OPPSTART MED GLUTENFRI DIETT

Irritabel tarm syndrom: Diagnose kriterier*	
Har du hatt tilbakevendende magesmerter/ubehag** i mer enn seks måneder?	Ja / Nei
Har plagene vært til stede i minst 3 dager per måned de siste 3 månedene?	Ja / Nei
Dersom Ja på minst ett av spørsmålene:	
To av følgende forhold må også være tilstede:	
1. Forsvinner magesmertene/ubehaget** når du vært på do?	Ja / Nei
2. Opplever du forandring i avførings frekvens ved symptomdebut?	Ja / Nei
3. Opplever du forandring i avføringens konsistens ved symptomdebut?	Ja / Nei
*Kriteriene gjelder for de siste 3 måneder med oppstart av symptomer seks måneder tidligere.	
**Med ubehag menes følelse som ikke beskrives som smerte.	

Hvordan endret plagene seg etter overgang til glutenfri kost?

Totalt sett, opplever du bedring på glutenfri kost?

Ja / Nei

Hvilke plager opplever du dersom du spiser gluten?

Magesmerter	Ja / Nei
Oppblåsthet	Ja / Nei
Diaré	Ja / Nei
Forstoppelse	Ja / Nei
Kvalme	Ja / Nei
Ledd/muskelsmerter	Ja / Nei
Hodepine	Ja / Nei
Hudkløe	Ja / Nei
Konsentrasjonsvansker	Ja / Nei
Prikking/nummenhet	Ja / Nei

ANDRE SYKDOMMER

Spesifiser eventuell sykdom	Har ikke hatt	Har hatt	Har nå

MEDIKAMENTER

Faste medikamenter

Preparat	Styrke	Fast dosering / Ved behov	Skal brukes under studien?

NB: Ikke kosttilskudd – det kommer fram i kostdagboken

Andre medikamenter som er brukt siste 30 dager

Preparat	Styrke	Fast dosering/ Ved behov	Skal brukes under studien?

Hvis deltaker ikke husker, be om å sjekke hjemme og ringe tilbake

Ja / Nei

Baseline symptomer

Fylt ut spørreskjemaer for Baseline:		Score
GSRs-IBS	Ja / Nei	
SHC	Ja / Nei	
SF-36	Ja / Nei	
BDI-II	Ja / Nei	
HAD	Ja / Nei	
GBB-Fatigue	Ja / Nei	
VAS Baseline (gjennomsnitt totale plager i millimeter)	Ja / Nei	

NB: Samles inn og bearbeides! Sammenlignes med Wash Out.

Sjekk spm 9 i BDI og deltakeren har svart alternativ 0?

Ja / Nei

Hvis deltakeren har svart 1, 2 eller 3 skal lege kontaktes omgående.

Antropometri utføres på seksjon for klinisk ernæring:

Høyde _____ cm

Vekt _____ kg

BMI _____ m/kg²**Utført klinisk undersøkelse (lege)****Ja / Nei**

BT/Puls: _____

Cor/pulm/abdomen: _____

BAKGRUNNSINFORMASJON

Hvilket aktivitetsnivå har du?

Generelt:

1 Sengeliggende/inaktiv	2 Stillesittende arbeid	3 Stående arbeid	4 Fysisk hardt arbeid

Fritid:

1 Lite aktiv (< 2 timers fysisk aktivitet/uke)	2 Aktiv (2-3 timer aktivitet/uke)	3 Svært aktiv (> 3 timer fysisk aktivitet/uke)

Arbeidssituasjon (Sett ett kryss):

1 Skoleelev/student	
2 Hjemmeværende	
3 Yrkespraksis/lærling	
4 Militærtjeneste	
5 Arbeidssøkende/permittert	
6 Attføring/ufør	
7 Ansatt i offentlig virksomhet	
8 Ansatt i privat virksomhet	
9 Selvstendig næringsdrivende	
10 Familiemedlem uten fast lønn i familiebedrift (f.eks gårdsbruk, forretning)	

Annet: _____

Røyker du?

Ja/Nei

Hvis ja, oppgi mengde:

< 2 / dag (1)	3-6 / dag (2)	7-10 / dag (3)	>10 / dag (4)

Driker du alkohol?

Ja/Nei

En mengde = en alkoholenhet, tilsvarende 1 glass (1/3 l) øl, ett glass vin, 1 hetvinsglass (sherry/hetvin), 1drammeglass (brennevin/likør).

Hvis ja, oppgi mengde:

<1 /mnd (1)	1-3 /mnd (2)	1/ uka (3)	2-3 / uka (4)	4-5 / uka (5)	6-7 / uka (6)

Påminnelser før neste oppmøte:

SMS-Baseline: Påminnelse AFP 1

Ja / Nei

Avtalt tidspunkt for oppmøtene og blodprøvetaking hos bioingeniør?
NB! Ikke tirsdager

Ja / Nei

Dag	Dato 1	Tidspunkt	Evt Dato 2	Tidspunkt	Evt Dato 3	Tidspunkt
Prov 1						
Prov 2						
Prov 3						
Slutt						

Satt opp tid for neste oppmøte i innholdsfortegnelsen?

Ja / Nei

Gitt informasjon om kostdagbok

Ja / Nei

Gitt informasjon om daglig Baseline VAS?

Ja / Nei

Gitt informasjon om avføringsprøver?

Ja / Nei

Delt ut materiell til avføringsprøver?

Ja / Nei

Gitt informasjon om lang tid til avkodning (mulighet for 3 dagers prov etterpå)

Ja / Nei

Fulgt deltaker til blodprøvetaking?

Ja / Nei

Blodprøver Baseline:

Hb, hvite, trc, diff.telling, MCV, Na, K, kalsium, kreatinin, albumin, bilirubin, CRP, ALP, ASAT, ALAT, LD GT, jern, transferrin, ferritin, fritt-Ca, PTH, HbA1c, f-T4, TSH, vit-B12, folat, 25-OH vitamin D2. Anti-tTg (IgA), anti-deamidert gliadin-peptid (IgG), HLA-DQ2/DQ8.

Prøveglass til serum/cytokin. EDTA til biobank. PAX-gene. IgE hvete, Immunglob kvant.

ACD til immunologiske og genetiske analyser.

NB:

Utskrift av blodprøvesvar lagt ved CRF?

Ja / Nei

Utskrift av svar på gastroskopi lagt ved CRF?

Ja / Nei

Appendix 4: Food diary

Kostdagbok 7 dager sammenhengende registrering



Deltaker ID: _____

Fra dato: _____

Til dato: _____

Før du starter..

Alt som spises og drikkes skal registreres, også vann og pastiller. Jo flere detaljer desto bedre.

Skriv opp:

- Navn på matvaren/retten, helst spesifisert.
- Hvordan maten er tilberedt. Eks: Gulrøtter, kokte
- Angi mengde så nøyaktig som du kan.
Eks: I husholdningsmål: Dl, ss, ts, kopp osv.
I størrelse (om frukt og lignende): Liten, middels, stor.
- Hjemmelagede retter/oppskrifter kan skrives opp på ledig plass i heftet.
- Angi oppgitt mengde på en vare. Eks: 1/2 Kvikkklunsj á 46 g.
- Kosttilskudd. Eks: Vitamineral

Husk blant annet:

- Mengde sukker og melk i kaffe/te
- Mengde kanel/sukker og annet tilbehør på grøt og kornblanding
- Mengde majones på annet pålegg
- Mengde dressing på salat

Dersom det er for liten plass i tabellen for det enkelte måltidet, fullfør måltidet i annet og spesifiser klokkeslett og måltidstype.

SKRIV TYDELIG!

Mengden innhold i kopp/krus/glass som vanligvis brukes:

Fyll opp kopp/krus/glass med vann tilsvarende mengden væske som du vanligvis bruker. Hell vannet over i et desilitermål for å finne riktig mengde i ml. Fø opp antall ml nedenfor.

Eksempel 1:

Tekoppen du bruker rommer 150 ml. Ved registrering fører du opp at du har drukket 1½ kopp te. Ved beregning av inntaket vil man kunne regne ut at 1½ kopp te tilsvarer 225 ml.

Kopp _____ ml

Krus _____ ml

Glass _____ ml

Eksempel 2

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING
7:30	2 stk, à 2A	Glutenfritt grovbrød	Toro glutenfri, grov melblanding
	3D	Skinkeost (smøreost)	16 % fett, Kavli
	2 stk	Kokt skinke	Gilde
	1 glass, 1A	Juice	appelsin

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING
11:00	9B	Grønnsaker (spesifiser type grønnsaker)	Wokket
	9A	Brokkoli	Wokket
	1/2 9A	Paprika	Wokket
	1/2 stk	Gulrot	Wokket
	2 ss	Sweet chilisaus	Santa Maria
	1 ss	Glutenfri soyasaus	Kikkoman
	6B	Jasminris	Eldorado
	1 ss	Rapsolje	Til steking

KOSTREGISTRERING

DATO:.....

ID _____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID _____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID_____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID _____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

ID _____

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID_____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID _____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

DATO:.....

ID_____

Frokost

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Lunsj

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Mellommåltid/snack

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Middag/Dessert

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Kveldsmåltid

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Annet

KL	MENGDE	MATVARE/RETT/PRODUKTNAVN	TILBEREDNING

Appendix 5: Adherence questionnaire

Kef intervju – etterlevelse av glutenfri kost

1. De siste 6 månedene har jeg fulgt en glutenfri diett:

- Hele tiden
- Mesteparten av tiden
- Halvparten av tiden
- Litt av tiden
- Ikke i det hele tatt

2. Drikke du øl? Ja Nei Av og til

Hvis Ja eller Av og til, hvilke merker velger du?

3. Spiser du a) Vanlig brød? Ja Nei Av og til

b) Vanlig havre? Ja Nei Av og til

c) Spelt? Ja Nei Av og til

4. Dersom du har fått i deg gluten, opplever du symptomer?

Alltid Ofte Av og til Sjelden Aldri

5. Hvor ofte får du symptomer hvis du får i deg selv små mengder gluten, for eksempel brødsmler?

Alltid Ofte Av og til Sjelden Aldri

6. 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

8. 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

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

Alltid Ofte Av og til Sjelden Aldri

10. Dersom du er på ferie, hender det at du avviker fra den glutenfrie dietten?

Alltid Ofte Av og til Sjelden Aldri

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

Alltid Ofte Av og til Sjelden Aldri

12. Hvor ofte hender det at du spiser glutenholdig mat for å være høflig eller av hensyn til andre (sosiale sammenkomster)?

Alltid Ofte Av og til Sjelden Aldri

13. 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

Andre situasjoner (f.eks pga religiøse situasjoner): _____

14. Forstår du ingredienslister på produkter?

Alltid Ofte Av og til Sjelden Aldri

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

Alltid Ofte Av og til Sjelden Aldri

16. Klarer du å unngå gluten i uforutsette situasjoner?

Alltid Ofte Av og til Sjelden Aldri

17. Hender det at du avviker fra dietten når det er krevende å finne glutenfrie alternativer?

Alltid Ofte Av og til Sjelden Aldri

18. Etter min mening er det en utfordring å finne glutenfrie alternativer i hverdagen:

Enig Delvis enig Usikker Delvis uenig Uenig

19. Jeg føler jeg har god nok kunnskap til å mestre den glutenfrie dietten:

Enig Delvis enig Usikker Delvis uenig Uenig

20. I hvilken grad vil du si den glutenfrie kosten er viktig for helsen din?

Viktig Litt viktig Usikker Litt uviktig Ikke viktig

21. Hvordan vurderer du helsen din i forhold til personer som *ikke* har cøliaki?

Mye bedre Litt bedre Like god Litt dårligere Mye dårligere

Appendix 6: Knowledge test

Glutenfritt kosthold

Sett kryss ved riktig svar.

Deltaker ID _____

1. Hva er gluten?

a) Proteiner i korn?	
b) Stivelse i korn?	
c) En kornart?	

2. Hvilke kornsorter kan man **IKKE** spise på et glutenfritt kosthold?
(Flere svar er riktige)

a) Spelt	
b) Quinoa	
c) Rug	
d) Ris	
e) Bygg	
f) Havre	
g) Hvete	
h) Durumhvete	
i) Bokhvete	

3. Hvilke matvarer er det viktig å holde seg **unna** på et glutenfritt kosthold?
(Flere svar er riktige)

b) Knekkebrød, Wasa husmann	
c) Panert kjøtt og fisk	
d) Grovbrød	
e) Poteter	
g) Majones	
h) Couscous	
i) Speltkli	
j) Hvetestivelse	
k) Gomorgen yoghurt med müsli	
m) Nøtter	
n) Byggryn	

4. Er det nødvendig å sjekke om øl inneholder gluten?

a) Ja	
b) Nei	

5. Er det nødvendig å sjekke om supper inneholder gluten?

a) Ja	
b) Nei	

Appendix 7: Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome

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 7 SISTE DAGER. Sett kryss (X) ved det alternativet som passer best på deg og din situasjon.

Dato: _____

Deltaker ID: _____

1. Har du i løpet av den siste uken vært plaget av MAGESMERTER?

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

2. Har du i løpet av den siste uken vært plaget av SMERTER ELLER UBEHAG I MAGEN SOM GIR SEG NÅR DU HAR HATT AVFØRING?

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

3. Har du i løpet av den siste uken vært plaget av OPPBLÅSTHET?

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

4. Har du i løpet av den siste uken vært plaget av LUFTAVGANG?

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

5. Har du i løpet av den siste uken vært plaget av FORSTOPPELSE (problemer med å tømme tarmen)?

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

6. Har du i løpet av den siste uken vært plaget av DIARÉ (hyppig avføring)?

- 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 den siste uken 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 den siste uken 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 den siste uken vært plaget av TVINGENDE AVFØRINGSBEHOV (plutselig behov for å gå på toalettet for å tømme tarmen)?

113

- 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 den siste uken vært plaget av en FØLELSE AV UFULLSTENDIG TØMMING 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 den siste uken vært plaget av at du FØLER DEG METT LIKE ETTER AT DU HAR BEGYNT PÅ ET MÅLTID?

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

12. Har du i løpet av den siste uken vært plaget av at du FØLER DEG METT SELV LENGE ETTER AT DU ER FERDIG MED Å SPISE?

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

13. Har du i løpet av den siste uken vært plaget av at MAGEN ER SYNLIG OPPBLÅST?

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

KONTROLLER AT ALLE SPØRSMÅLENE ER BESVART!

TAKK FOR DIN MEDVIRKNING.

Appendix 8: 7-day visual analogue scale diary for gastrointestinal symptoms

Symptomdagbok – Registrering av ulike plager

Symptomregistreringen skal fylles ut ved å sette **én** loddrett strek på linjen etter det som passer best med hvordan du har det. Denne dagboken skal fylles ut HVER DAG. For eksempel:

Lite magesmerte _____ | _____ Mye magesmerte

Dato: _____

Lite magesmerte _____ Mye magesmerte

Lite oppblåsthet _____ Mye oppblåsthet

Lite luftavgang _____ Mye luftavgang

Lite kvalme _____ Mye kvalme

Fornøyd med avføringsmønster _____ Ikke fornøyd med avføringsmønster

Lite plager totalt _____ Mye plager totalt

Dato: _____

Lite magesmerte _____ Mye magesmerte

Lite oppblåsthet _____ Mye oppblåsthet

Lite luftavgang _____ Mye luftavgang

Lite kvalme _____ Mye kvalme

Fornøyd med avføringsmønster _____ Ikke fornøyd med avføringsmønster

Lite plager totalt _____ Mye plager totalt

Dato: _____

Lite magesmerte _____ Mye magesmerte

Lite oppblåsthet _____ Mye oppblåsthet

Lite luftavgang _____ Mye luftavgang

Lite kvalme _____ Mye kvalme

Fornøyd med avføringsmønster _____ Ikke fornøyd med avføringsmønster

Lite plager totalt _____ Mye plager totalt

Dato: _____

Lite magesmerte	_____	Mye magesmerte
Lite oppblåsthet	_____	Mye oppblåsthet
Lite luftavgang	_____	Mye luftavgang
Lite kvalme	_____	Mye kvalme
Fornøyd med avføringsmønster	_____	Ikke fornøyd med avføringsmønster
Lite plager totalt	_____	Mye plager totalt

Dato: _____

Lite magesmerte	_____	Mye magesmerte
Lite oppblåsthet	_____	Mye oppblåsthet
Lite luftavgang	_____	Mye luftavgang
Lite kvalme	_____	Mye kvalme
Fornøyd med avføringsmønster	_____	Ikke fornøyd med avføringsmønster
Lite plager totalt	_____	Mye plager totalt

Dato: _____

Lite magesmerte	_____	Mye magesmerte
Lite oppblåsthet	_____	Mye oppblåsthet
Lite luftavgang	_____	Mye luftavgang
Lite kvalme	_____	Mye kvalme
Fornøyd med avføringsmønster	_____	Ikke fornøyd med avføringsmønster
Lite plager totalt	_____	Mye plager totalt

Dato: _____

Lite magesmerte	_____	Mye magesmerte
Lite oppblåsthet	_____	Mye oppblåsthet
Lite luftavgang	_____	Mye luftavgang
Lite kvalme	_____	Mye kvalme
Fornøyd med avføringsmønster	_____	Ikke fornøyd med avføringsmønster
Lite plager totalt	_____	Mye plager totalt

Appendix 9: Giessen Subjective Complaint List

Giessener Beschwerdebogen (GBB)

Se tilbake på hvordan du har hatt det **den siste uken** og sett **ett kryss** for hvert av de seks spørsmålene.

Dato: _____

Deltaker ID _____

Jeg føler meg belastet med følgende plager.

1. Slapphet/svakhet

Ikke Sterkt Muligens litt Noe Betydelig

2. Overdrevent søvnbehov

Ikke Sterkt Muligens litt Noe Betydelig

3. Fort sliten/utmattet

Ikke Sterkt Muligens litt Noe Betydelig

4. Tretthet

Ikke Sterkt Muligens litt Noe Betydelig

5. Følelse av å være ”utenfor” eller fortumlet

Ikke Sterkt Muligens litt Noe Betydelig

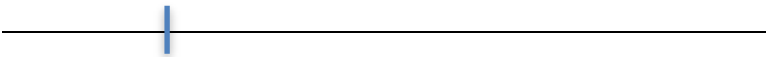
6. Følelse av utmattelse

Ikke Sterkt Muligens litt Noe Betydelig

Appendix 10: Giessen Subjective Complaint List – visual analogue scale

Symptomregistrering (VAS-GBB)

Se tilbake på **den siste uken** og sett **én** loddrett strek på linjen for å beskrive hvordan du har hatt det.
For eksempel:

Lite slapp		Mye slapp
Lite slapp/svak	<hr/>	Mye slapp/svak
Lite plaget av overdrevent søvnbehov	<hr/>	Mye plaget av overdreven søvnbehov
Lite plaget av fort sliten/utmattet	<hr/>	Mye plaget av fort sliten/utmattet
Lite trett	<hr/>	Mye trett
Lite ”utenfor” eller fortumlet	<hr/>	Mye ”utenfor” eller fortumlet
Lite utmattet	<hr/>	Mye utmattet
Lite følelse av nummenhet i hender og føtter	<hr/>	Mye følelse av nummenhet i hender og føtter
Lite følelse av prikking i hender og føtter	<hr/>	Mye følelse av prikking i hender og føtter
Lite opplevelse av manglende fokus (konsentrasjon)	<hr/>	Mye opplevelse av manglende fokus (konsentrasjon)
Lite ledd og muskelsmerter	<hr/>	Mye ledd og muskelsmerter
Lite deprimert	<hr/>	Veldig deprimert

Appendix 11: Beck Depression Inventory-II

BDI-II

Dato _____

Deltaker ID _____

Se tilbake på den siste uken og sett ring rundt det alternativet som passer best.

1 Tristhet

0. Jeg føler meg ikke trist
1. Jeg føler meg trist store deler av tiden
2. Jeg føler meg trist hele tiden
3. Jeg er så trist eller ulykkelig at jeg ikke holder det ut

2 Pessimisme

0. Jeg er ikke motløs med tanke på fremtiden
1. Jeg er mer motløs med tanke på fremtiden enn jeg var før
2. Jeg forventer at ting ikke vil gå i orden for meg
3. Jeg føler at fremtiden min er håpløs, og at alt bare vil verre

3 Mislykkethet

0. Jeg føler meg ikke mislykket
1. Jeg har mislyktes mer enn jeg burde
2. Når jeg ser tilbake, ser jeg mange nederlag
3. Jeg føler meg som en fullstendig mislykket person

4 Tap av glede

0. Jeg får like mye glede ut av ting jeg liker som før
1. Jeg får ikke like mye glede ut av ting som før
2. Jeg får svært liten glede ut av de tingene som jeg pleide å like
3. Jeg får ingen glede ut av de tingene som jeg pleide å like

5 Skyldfølelse

0. Jeg føler ikke særlig mye skyld
1. Jeg føler skyld for mange ting jeg har gjort eller burde gjøre
2. Jeg føler skyld mesteparten av tiden
3. Jeg føler skyld hele tiden

6 Følelse av å bli straffet

0. Jeg føler ikke at jeg blir straffet
1. Jeg føler det som om jeg kan bli straffet
2. Jeg forventer å bli straffet
3. Jeg føler det som om jeg blir straffet

7 Mislike seg selv

0. Mitt selvbilde er uforandret
1. Jeg har fått mindre selvtillit
2. Jeg er skuffet over meg selv
3. Jeg misliker meg selv

8 Selvkritikk

0. Jeg kritiserer eller bebreider ikke meg selv mer enn vanlig
1. Jeg kritiserer meg selv mer enn jeg pleide
2. Jeg kritiserer meg selv for alle mine feil
3. Jeg klandrer meg selv for alt leit som skjer

9 Selvmordstanker

0. Jeg har ingen tanker om å ta livet mitt
1. Jeg har tanker om å ta livet mitt, men ingen planer om å gjøre det
2. Jeg ønsker å ta livet mitt
3. Jeg ville tatt livet mitt dersom jeg fikk mulighet til det

10 Gråt

0. Jeg gråter ikke mer enn før
1. Jeg gråter mer enn før
2. Jeg gråter for hver minste ting
3. Jeg ønsker å gråte, men klarer det ikke

11 Rastløshet

0. Jeg er ikke mer rastløs eller urolig enn vanlig
1. Jeg føler meg mer rastløs eller urolig enn vanlig
2. Jeg er så rastløs og urolig at det er vanskelig å være i ro
3. Jeg er så rastløs og urolig at jeg må bevege meg eller gjøre noe hele tiden

12 Tap av interesse

0. Jeg har ikke mistet interesse for andre mennesker eller aktiviteter
1. Jeg er mindre interessert i andre mennesker eller ting enn tidligere
2. Jeg har mistet det meste av min interesse for andre mennesker eller ting
3. Det er vanskelig å bli interessert i noe som helst

13 Ubesluttsomhet

0. Jeg tar beslutninger like lett som før
1. Jeg synes det er vanskeligere å ta beslutninger nå enn før
2. Jeg har mye større vanskeligheter med å ta beslutninger nå enn før
3. Jeg har vanskeligheter med å ta enhver beslutning.

14 Verdiløshet

0. Jeg føler meg ikke verdiløs
1. Jeg opplever meg ikke like verdifull og nyttig som før
2. Jeg føler meg mer verdiløs enn andre mennesker
3. Jeg føler meg fullstendig verdiløs

15 Tap av energi

0. Jeg har like mye energi som før
1. Jeg har mindre energi enn jeg pleide
2. Jeg har ikke nok energi til å gjøre særlig mye
3. Jeg har ikke nok energi til å gjøre noe som helst

16 Endringer i søvnmønster

- 0 Jeg har ikke merket noen endringer med søvnen min
- 1a Jeg sover litt mer enn vanlig
- 1b Jeg sover litt mindre enn vanlig
- 2a Jeg sover mye mer enn vanlig
- 2b Jeg sover mye mindre enn vanlig
- 3a Jeg sover mesteparten av døgnet
- 3b Jeg våkner opp 1-2 timer for tidlig, og får ikke sove igjen

17 Irritabilitet

- 0. Jeg er ikke mer irritabel enn vanlig
- 1. Jeg er mer irritabel enn vanlig
- 2. Jeg er mye mer irritabel enn vanlig
- 3. Jeg er irritabel hele tiden

18 Endringer i matlysten

- 0 Jeg har ikke merket noen endringer i min matlyst
- 1a Min matlyst er litt mindre enn vanlig
- 1b Min matlyst er litt større enn vanlig
- 2a Min matlyst er mye mindre enn vanlig
- 2b Min matlyst er mye større enn vanlig
- 3a Jeg har ingen matlyst i det hele tatt
- 3b Jeg føler trang til å spise hele tiden

19 Konsentrasjonsvansker

- 0. Jeg kan konsentrere meg like bra som før
- 1. Jeg kan ikke konsentrere meg like godt som før
- 2. Det er vanskelig for meg å konsentrere meg om noe som helst særlig lenge
- 3. Jeg merker at jeg ikke kan konsentrere meg om noe som helst

20 Tretthet og utmattelse

- 0. Jeg er ikke mer trøtt eller utmattet enn jeg pleier
- 1. Jeg blir fortere trøtt eller utmattet enn jeg pleier
- 2. Jeg er for trøtt eller utmattet til å gjøre mange av de tingene jeg pleide å gjøre
- 3. Jeg er for trøtt eller utmattet til å gjøre mesteparten av de tingene jeg pleide å gjøre

21 Tap av seksuell interesse

- 0. Jeg har ikke merket noen endring i min interesse for sex i det siste
- 1. Jeg er mindre interessert i sex enn jeg pleier
- 2. Jeg er mye mindre interessert i sex nå
- 3. Jeg har mistet all interesse for sex

Appendix 12: Subjective Health Complaints

Nedenfor nevnes noen alminnelige helseproblemer (sett ring rundt tallet som passer)		Ikke plaget	Litt plaget	Endel plaget	Alvorlig plaget
1.	Forkjølelse, influensa	0	1	2	3
2.	Hoste, bronkitt	0	1	2	3
3.	Astma	0	1	2	3
4.	Hodepine	0	1	2	3
5.	Nakkesmerter.....	0	1	2	3
6.	Smerter øverst i ryggen.....	0	1	2	3
7.	Smerter i korsrygg	0	1	2	3
8.	Smerter i armer	0	1	2	3
9.	Smerter i skuldre.....	0	1	2	3
10.	Migrene	0	1	2	3
11.	Hjertebank, ekstraslag.....	0	1	2	3
12.	Brystsmerter	0	1	2	3
13.	Pustevansker	0	1	2	3
14.	Smerter i føttene ved anstrengelser	0	1	2	3
15.	Sure oppstøt, «halsbrann»	0	1	2	3
16.	Sug eller svie i magen.....	0	1	2	3
17.	Magekatarr, magesår	0	1	2	3
18.	Mageknip	0	1	2	3
19.	«Luftplager».....	0	1	2	3
20.	Løs avføring, diaré	0	1	2	3
21.	Forstoppelse.....	0	1	2	3
22.	Eksem	0	1	2	3
23.	Allergi.....	0	1	2	3
24.	Hetetokter	0	1	2	3
25.	Søvnproblemer	0	1	2	3
26.	Tretthet	0	1	2	3
27.	Svimmelhet.....	0	1	2	3
28.	Angst	0	1	2	3
29.	Nedtrykt, depresjon	0	1	2	3

Tilleggspørsmål dersom du har angitt flere helseproblemer:

Hvilket av disse problemene har vært mest plagsomt for deg den siste uken?.....

Appendix 13: Short Form-36

2439620017 Versjon Glutenstudiene Rikshospitalet 2014 SF-36 1/4

Rikshospitalet - Radiumhospitalet HF

Glutenstudiene 2014

Dato: . .

Deltaker ID:

SF-36

Dette spørreskjemaet spør om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål. Hvert spørsmål skal besvares ved å sette et kryss i boksen for det alternativet som passer best for deg. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan på alle spørsmålene.

1. Stort sett vil du si at din helse er:
- Utmerket
 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 løpe, 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 flytte et bord, støvsuge, gå 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 handlekurv
- Ja, begrenser meg mye. Ja, begrenser meg litt. Nei, begrenser meg ikke i det hele tatt.
- D. Gå opp trappen flere etasjer
- 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. Gå mer enn to kilometer

- Ja, begrenser meg mye. Ja, begrenser meg litt. Nei, begrenser meg ikke i det hele tatt.

H. Gå noen hundre meter

- Ja, begrenser meg mye. Ja, begrenser meg litt. Nei, begrenser meg ikke i det hele tatt.

I. Gå 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 den siste uken, 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. fordi det krevde ekstra anstrengelser)? Ja Nei

5. I løpet av den siste uken, har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (f. eks. fordi du har følt deg deprimeret 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 den siste uken, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

- Ikke i det hele tatt Litt Endel Mye Svært mye





7. Hvor sterke kroppslige smerter har du hatt i løpet av den siste uken?

- | | |
|--------------------------------------|---------------------------------------|
| <input type="checkbox"/> Ingen | <input type="checkbox"/> Moderate |
| <input type="checkbox"/> Meget svake | <input type="checkbox"/> Sterke |
| <input type="checkbox"/> Svake | <input type="checkbox"/> Meget sterke |

8. I løpet av den siste uken, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

- | | |
|---|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |
| <input type="checkbox"/> Endel av tiden | |

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

A. Følt deg full av tiltakslyst?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

B. Følt deg veldig nervøs?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

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

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

D. Følt deg rolig og harmonisk?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

E. Hatt mye overskudd?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

F. Følt deg nedenfor og trist?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

G. Følt deg sliten?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

H. Følt deg glad?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> Ikke i det hele tatt |

I. Følt deg trett?

- | | |
|--|---|
| <input type="checkbox"/> Hele tiden | <input type="checkbox"/> Endel av tiden |
| <input type="checkbox"/> Nesten hele tiden | <input type="checkbox"/> Litt av tiden |
| <input type="checkbox"/> Mye av tiden | <input type="checkbox"/> 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.)?

- Hele tiden Endel av tiden
 Nesten hele tiden Litt av tiden
 Mye av tiden Ikke i det hele tatt

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

	Helt riktig	Delvis	Vet ikke	Delvis galt	Helt galt
A) Det virker som om jeg blir lettere syk enn andre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B) Jeg er like frisk som de fleste jeg kjenner	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C) Jeg forventer at min helse vil bli dårligere	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
D) Min helse er utmerket	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Appendix 14: Supplementary results – supplements used by participants

Table S2. Supplements used by participants. Number (%), n=56

	n	%
Cod-liver oil ^a	15	(27)
Vitamin D	11	(20)
Multivitamin	10	(18)
Calcium	5	(9)
Magnesium	5	(9)
B vitamins	5	(9)
Iron	4	(7)
Vitamin C	4	(7)
Probiotics	4	(7)
Vitamin K	3	(5)
Selenium	3	(5)
Iodine	2	(4)
Zinc	2	(4)
Protein supplement	2	(4)
Less common supplements ^a	1	(2)

^aIncluded in the analysis of the food diaries in *the Diet Planner*

^bVitamin E, vitamin A, chrome, glutamine, collagen, glucosamine, BioQ10, licorice root, garlic, African mango, echinacea, and Kamut (khorasan) grains.

Appendix 15: Supplementary results – less-common food avoidances

Foods that were excluded by one participant (2 %):

- Eggs
- Yeast
- Artificial sweeteners
- Quickly absorbed carbohydrates
- Seafood
- Fish
- Shellfish
- Nuts
- Peanuts
- Chestnuts
- Potatoes
- Rice
- Raw vegetables
- Tomatoes
- Red wine
- Soft cheeses
- Strawberries
- Curry sauce
- Soya sauce
- Bananas
- Pasta
- Bread
- Sugar-free chewing-gum
- Chillies
- Red meat
- Oranges
- Kiwi fruit

Appendix 16: Supplementary results – additional diseases

Table S4. Less-common diseases present in NCGS patients.
Number (%), n=66.

	n (%)
Asthma and allergies	12 (18)
Cardiovascular conditions	7 (11)
ME (Chronic Fatigue Syndrome)	4 (6)
Fibromyalgia	4 (6)
Migraine	4 (6)
Other ^a	18 (27)

Abbreviation: ME: myalgic encephalomyelitis

^aOther diseases, ≤ 2 NCGS patients; fatigue, depression, panic anxiety, irritable bowel syndrome, osteoporosis, reflux, type 1 diabetes, Attention Deficit Hyperactivity Disorder, carpal tunnel syndrome, chronic tendonitis in foot, nerve damage in foot, elevated blood glucose levels, endometriosis, herpes simplex virus, sciatica, lichen planus, lichen sclerosis, monoclonal gammopathy, vitiligo

Appendix 17: Supplementary results – laboratory values of nutritional biomarkers

Table S5. Laboratory values for NCGS females and males, with respective reference values. Mean (SD) and median (Q₁, Q₃)

Laboratory values	Females (n=58)				Males (n=8)			
	n	Mean (SD)	Median (Q ₁ ,Q ₃)	Reference values	n	Mean (SD)	Median (Q ₁ ,Q ₃)	Reference values
Haemoglobin (g/dL)	58	13.78 (0.9)	13.7 (13.2, 14.2)	11.7–15.3	8	15.2 (1.2)	15.5 (15.3, 15.9)	13.4–17.0
Iron (µmol/L)	58	17.3 (5.8)	15.5 (13.0, 21.0)	9.0–34.0	8	18.1 (4.1)	19.5 (14.5, 21.5)	9.0–34.0
Ferritin (µg/L)	58	78.0 (47.1)	67.0 (43.8, 108.0)	10–170	8	164.1 (86.7)	177.5 (72.3, 247.8)	30–400
Transferrin (g/L)	58	2.6 (0.35)	2.6 (2.4, 2.8)	2.0–3.3	8	2.5 (0.37)	2.5 (2.2, 2.8)	2.0–3.3
Free calcium (mmol/L)	57	1.2 (0.04)	1.2 (1.2, 1.3)		8	1.4 (0.3)	1.3 (1.2, 1.3)	
Vitamin B ₁₂ (pmol/L)	56	474.7 (216.7)	433.5 (324.0, 588.0)	150–650	8	373.6 (268.3)	305.0 (221.8, 367.0)	150–650
Folic acid, B9 (nmol/L)	58	25.5 (8.9)	25.5 (17.8, 32.3)	≥7	8	29.6 (13.1)	29.0 (17.5, 42.8)	≥7
25-OH-vit.D (nmol/L)	56	70.1 (18.8)	69.5 (58.0, 79.8)	25-131	7	62.0 (18.6)	63.0 (45.0, 69.0)	25-131
HbA _{1c} (%)	56	5.3 (0.5)	5.2 (5.0, 5.5)	4.0–6.0	7	5.4 (0.3)	5.4 (5.2, 5.7)	4.0–6.0
TSH ^b (x10E-3 IU/L)	58	1.3 (0.9)	1.3 (0.6, 1.8)	0.5–3.6 ^a	8	1.6 (0.5)	1.6 (1.3, 1.9)	0.5–3.6 ^a
FT4 (pmol/L)	58	15.3 (3.0)	15.0 (14.0, 17.0)	8.0–21.0 ^a	8	15.9 (1.9)	16.0 (14.3, 17.5)	8.0–21.0 ^a
PTH (pmol/L)	57	5.0 (2.6)	4.2 (3.5, 6.0)	1.5–7.0 ^a	8	4.4 (1.7)	4.2 (3.1, 5.6)	1.5–7.0 ^a

Abbreviations: 25-OH vit. D; 25-hydroxy vitamin D, HbA_{1c}; glycated haemoglobin A_{1c}, TSH;

Thyroidea stimulating hormone, FT4; Free thyroxin, PTH; parathyroidea hormone

^aReference levels differ with age; reference values noted here are based on average age for the total sample (mean 44 years, range 21-72)

^bValues specified as <0.01 were entered as 0.01 (NCGS females, n=4)

Appendix 18: Supplementary results – energy percentages for the energy-providing nutrients, total NCGS sample

Table S3. Intake of energy-providing nutrients as percentage of total energy intake, females and males. Mean (SD), and median (Q₁, Q₃), n=56

Energy percentage from nutrients, E %	NCGS (n=56)		NNR12
	Mean (SD)	Median (Q ₁ , Q ₃)	
Protein	17.4 (4)	<i>17 (15, 19)</i>	10–20
Fat	43.4 (10)	<i>42 (36.3, 50)</i>	25–40
Saturated fatty acids	16.0 (7)	<i>14 (12, 18)</i>	<10
Trans-saturated fatty acids	0.1 (0.4)	<i>0 (0, 0)</i>	<1
Monounsaturated fatty acids	15.2 (5)	<i>14 (12, 18)</i>	10–20
Polyunsaturated fatty acids	6.6 (3)	<i>6 (4.3, 9)</i>	5–10
Carbohydrates	39.3 (10)	<i>40 (32, 46)</i>	45–60
Added sugar	5.6 (4)	<i>5 (3, 9)</i>	<10
Dietary fibre ^b	20.7 (10)	<i>18.9 (14.1, 23)</i>	25–35
Alcohol ^b	5.8 (8)	<i>1.9 (0,10)</i>	<10

Abbreviations: SD; standard deviation, Q₁, Q₃; 25th–75th percentile, NNR12; Nordic Nutrition Recommendations 2012, E %; energy percent. Values in *italic font* are non-parametric, median should be readed.

^aCarbohydrates, including dietary fibre

^bin grammes (g)

Appendix 19: Supplementary results – nutrient density

Nutrient density

Calculations of nutrient density are shown below in Table S1. In NCGS females, low nutrient density (nutrients reported/ energy intake reported, MJ < RI/EER, MJ) was seen for fibre, vitamin D, folic acid, iron, and iodine. In NCGS males, low nutrient density was seen for fibre, vitamin A, vitamin D, folic acid, calcium, magnesium and iodine. When compared to the average Norwegian population (Norkost 3) (117) by nutrient density per 10 MJ, NCGS patients had lower nutrient density for vitamin A, vitamin D, niacin, vitamin B₆, folic acid, vitamin C, calcium, iron, magnesium and zinc. Nutrient density of vitamin D, B₁₂, vitamin C, selenium, phosphorus was similar to the average Norwegian population. This suggests that NCGS patients are consuming food items containing fewer nutrients than recommended and compared to the average Norwegian population, following a diet with poorer quality. In comparison a study calculating nutrient density for newly diagnosed CD patients found that 10 % of patients had low nutrient density (92).

Calculating nutrient density enables us to compare dietary quality irrespective of energy intake. This is particularly valuable when suspecting underreporting and when comparing dietary intake between different dietary recording methods. This method increases the validity of the results from dietary data in this study.

Table S1. Nutrient density for vitamin and minerals compared to target nutrient intake/EER and nutrient density per 10 MJ in the average Norwegian diet (Norkost 3). EER`s are reference intakes from NNR12 (117).

Nutrients	Females (n=48)		Males (n=8)		Females and males (n=56)	Nutrient density per 10 MJ in Norkost 3
	Nutrients _{eat} ^a / MJ _{eat} (7.4 MJ ^b)	Nutrients _{rec.} / EER ^b (8.8 MJ)	Nutrients _{eat} / MJ _{eat} (9.4 MJ) ^a	Nutrients _{rec.} / EER (11.0 MJ)	Nutrient density/10 MJ ^a	
Fibre (gram)	2.6	3.0	2.2	3.0	24.5	-
Vitamin A (RAE ^f)	83.8	79.5	62.1	81.8	797	1117
Vitamin D (µg)	0.9 ^c	1.1	0.6 ^c	0.9	8.4 ^c	8.8
Vitamin E (α-TE ^g)	1.7	0.9	1.3	0.7	16.4	15.8
Thiamin (mg)	0.1	0.1	0.1	0.1	1.6	1.5
Riboflavin (mg)	0.2 ^b	0.1	0.2	0.1	2.1 ^b	1.9
Niacin (mg)	2.2	1.6	2.2	1.6	22	43
Vitamin B6 (mg)	0.2	0.1	0.2	0.1	2.1	2.5
Vitamin B12 (µg)	0.7	0.2	0.6	0.2	7.0	6.9
Folic acid (µg)	28.1	34.1	22.2	27.3	270	349
Vitamin C (mg)	13.0	8.5	9.5	6.8	123	132
Calcium (mg)	93.8	90.9	61.6	72.7	863	1114
Iron (mg)	1.1	1.7	1.0	0.8	10.6	13.1
Magnesium (mg)	37.7	31.8	29.5	31.8	362	419
Sodium (g)	0.3	0.3	0.2	0.2	2.5	-
Potassium (g)	0.4	0.4	0.3	0.3	3.8	4.0
Zinc (mg)	1.1	0.8	1.0	0.8	10.6	13.1
Selenium (µg)	5.8	5.7	5.5	5.5	58	58
Copper (mg)	0.1	0.1	0.1	0.1	1.4	-
Phosphorus (mg)	168.1	68.2	145.9	54.5	1657	1697
Iodine (µg)	10.3	17.0	6.6	13.6	95.6	-

Abbreviations: NNR12, Nordic nutrition recommendations 2012; Eat., eaten; Rec., recommended; MJ, mega joule; EER, estimated energy requirements.

^aMedian values are basis for the calculations

^bMean values are basis for the calculations

^cCod-liver oil is included in the calculations of the relative intakes

