Non-coeliac gluten sensitivity and coeliac disease

Dietary and diagnostic aspects

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SUMMARY

Non-coeliac gluten sensitivity (NCGS) is a term within gluten-related disorders applied for the condition described by symptom relief on gluten-free diet in absence of coeliac disease and wheat allergy. An important characteristic is the experience of gastrointestinal and extra intestinal symptoms after intake of gluten containing food. There are no reliable diagnostic biomarkers. Expert consensus meetings have legitimized NCGS and proposed standardised, blinded, placebo-controlled gluten challenge with defined cut-offs for symptom change as a diagnostic tool. Yet the topic remains highly controversial. The role of gluten is particularly debated since gluten challenge studies have shown conflicting results. Our aim was first to study the adherence to gluten-free diet in coeliac disease and non-coeliac subjects, secondly, to evaluate diagnostic methods in both conditions, and finally, to investigate the separate effect of gluten and fructan in subjects with self-reported NCGS.

We found that gluten-free diet adherence did not differ between coeliac disease and NCGS subjects. Diet adherence was fair to good in NCGS even though most of them were self-educated in gluten-free diet. In open wheat challenges in subjects with presumed NCGS where a gastroenterologist evaluated symptom change without predefined cut-offs, 85 % of the subjects had the suspicion of NCGS confirmed clinically. Interestingly, two proposed scoring systems for the evaluation of NCGS gave lower percentage of diagnosis compared to the gastroenterologist's evaluation. A 14-day gluten challenge of coeliac disease subjects showed the biological effects of a gluten containing muesli bar developed for challenge of NCGS subjects. The challenge was inadequate as diagnostic procedure for coeliac disease when villous blunting or increased coeliac disease specific antibody levels were used as outcome measures. Finally, we performed a randomised, double-blinded, placebo-controlled crossover challenge and found that fructan induced more gastrointestinal symptoms than gluten and placebo. Only four of 59 individuals had a symptomatic response compatible with NCGS, 24 had a pattern compatible with fructan inducible symptoms, whereas 22 in fact had their highest response to the placebo bar.

In conclusion, subjects with coeliac disease and self-reported NCGS adhered similarly to the gluten-free diet. Open wheat challenge with clinician-evaluation of symptom change in subjects with presumed NCGS overestimated the diagnosis as compared to suggested criteria. Also, gluten challenge of 14 days in subjects with coeliac disease in remission was too short to induce diagnostic changes, but proved the efficacy of the gluten. Finally, fructan emerged as the culprit that induced most gastrointestinal symptoms in subjects with self-reported NCGS. Our results illustrate the inadequacy of double-blinded, placebo-controlled food challenge as a diagnostic tool. They further question the entity NCGS and suggest that the condition should be regarded as a variant of irritable bowel syndrome.

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ABBREVIATIONS

ATI	Amylase trypsin inhibitor
BMR	Basal metabolic rate
CDAT	Coeliac disease adherence test
CI	Confidence interval
CSI	Coeliac symptom index
DBPCFC	Double-blind placebo-controlled food challenge
DGP	Deamidated gliadin-peptide
FODMAP	Fermentable oligo-, di-, monosaccharides and polyols
GBB	Giessen subjective complaint list
GSRS	Gastrointestinal symptom rating scale
HAD	Hospital anxiety and depression scale
HLA	Human leukocyte antigen
HRQoL	Health related quality of life
IBS	Irritable bowel syndrome
IEL	Intraepithelial lymphocytes
Ig	Immune globulin
IQR	Interquartile range
m-RNA	Messenger ribonucleic acid
NCGS	Non-coeliac gluten sensitivity
RCT	Randomised clinical trial
SD	Standard deviation
SF-36	Short Form-36
TG2	Tissue transglutaminase 2
VAS	Visual analogue scale
Vh/Cd	Villous height to crypt depth ratio
WA	Wheat allergy

1 INTRODUCTION

1.1 Food hypersensitivity

Food hypersensitivity is a frequently reported condition in the western world. It causes people to exclude single or several foods from the diet in order to obtain symptom relief or better health. An emerging trend has been people on elimination diets without necessarily well-founded medical indications, such as the milk-free diet and the wheat- or gluten-free diet. In western countries 15-20 % of the population perceives some form of food intolerance [1]. Approximately 20 % of the population alters the diet on the suspicion of an adverse reaction to food or a food component, although the prevalence of food allergy based on oral food challenge is only 1-2 % [2-5]. In people with functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), 50-84 % perceives their symptoms are related to food intake [6-8]. Diet restrictions may have impact on nutritional status and cause malnutrition or deficiency of certain nutrients if not managed or supplemented adequately. Deviant diets may also affect quality of life and private economy.

Food hypersensitivity is generally either immunological such as food allergy, or non-immunological without activation of the immune system, often termed food intolerance (Figure 1) [9, 10]. Wheat allergy and coeliac disease are examples of immunological conditions and lactose intolerance is a non-immunological food hypersensitivity. Food allergies are most often diagnosed easily by blood tests[11]. In contrast, food intolerances, mostly lack objective biomarkers in the clinical workup.

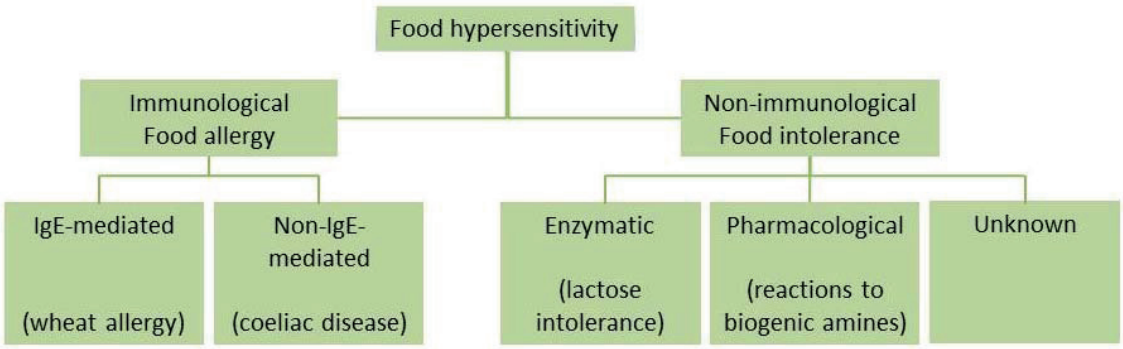

Figure 1 Classification of food hypersensitivity.

The medical investigation of suspected food intolerances ideally takes place in a multidisciplinary context where exclusion of other potential disease is crucial. Further, the workup includes a thorough medical history with dietary and lifestyle assessment focused on potential diet-related symptoms,

preferably by an experienced dietitian. The standard food intolerance test is food exclusion followed by systematic reintroduction and subsequent symptom induction to identify tolerance threshold (Figure 2) [12-14]. Reintroduction or challenge can be done either open or blinded depending on the nature of the symptoms. The gold standard diagnostic method is the double-blind placebo-controlled food challenge (DBPCFC). Objective acute onset symptoms like skin rash is more suitable for open challenge than subjective late onset symptoms [15]. In contrast to food allergy the food exclusion in food intolerance is based on reduction rather than complete exclusion. The method is often not straightforward and avoiding several dietary components may be required. When a restricted diet is indicated for long-term management, it should be supervised by a dietitian to avoid unnecessary restrictions and reduce the risk of nutritional deficiencies [16].

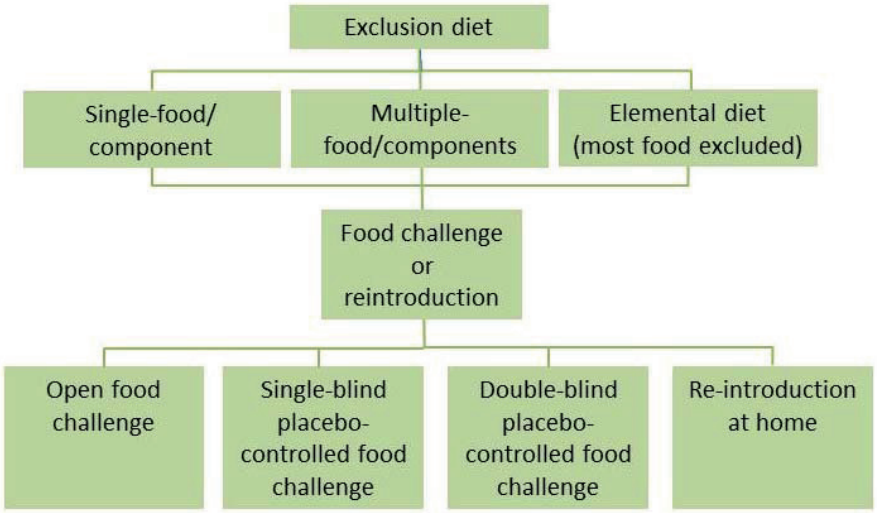

Figure 2 Food elimination and reintroduction in food hypersensitivity

1.2 Wheat – and gluten related disorders

Gluten and wheat are the main drivers of coeliac disease and wheat allergy. Unlike food intolerances, these two conditions have well-defined epidemiology, pathogenic mechanisms, diagnostic markers and treatment (Table 1) [17, 18]. Wheat allergy is defined by an immune globuline (Ig) E-mediated immune reaction in response to wheat ingestion and requires complete elimination of wheat from the diet. Wheat can also precipitate as a trigger of wheat-dependent exercise-induced anaphylaxis [19]. Those who are affected are asymptomatic except when wheat is consumed in close proximity to exercise. Coeliac disease is caused by an abnormal immune response to gluten proteins in wheat, rye and barley and requires a strict and lifelong gluten-free diet [20, 21]. IBS is a functional gastrointestinal disorder in which symptoms may improve in response to dietary restrictions which may include wheat or gluten [7]. Here, the pathogenic mechanism is more obscure. Later sections will describe coeliac

disease and IBS in depth. The last decade there has been a worldwide increase of people with self-diagnosed gluten sensitivity with clinical manifestations similar to coeliac disease but without the enteropathy or serologic features of coeliac disease, and without wheat allergy. They report improvement of gastrointestinal and extra-intestinal health in response to a self-instituted gluten-free diet. A definition paper of 2012 suggested including "non-coeliac gluten sensitivity" (NCGS) in the term of gluten-related disorders [22]. Although the gluten-specificity has not been proven, the term has been used since. The true prevalence is unknown and estimates from some prevalence studies range from 0.6 % to 10.6 % [23, 24].

Table 1 Disorders with confirmed and suggested relation to wheat and gluten

Disease	Prevalence (%)	Biomarker	Diagnostics	Management
Wheat allergy	0.1	IgE antibody	IgE + DBPCFC	Wheat-free diet
Coeliac disease	1	TG2-IgA	Duodenal biopsy	Gluten-free diet
IBS	10-20	-	Clinical assessment	Lifestyle, diet, medication
NCGS	0.6-10	-	-	Gluten-free diet

DBPCFC; double-blind placebo-controlled food challenge, IBS; irritable bowel syndrome, Ig; immunoglobulin, NCGS; non-coeliac gluten sensitivity, TG2; transglutaminase 2

Overlapping diagnosis

Approximately 20-30 % of treated coeliac disease patients present with IBS symptoms, and the two conditions coexist in some patients [25-27]. Guidelines therefore recommend excluding coeliac disease in all patients referred with IBS [28-31] . Figure 3 demonstrates the overlap between coeliac disease, IBS, NCGS and wheat allergy and presents the two main views about NCGS as an independent entity (Figure 3A) [32-35] or a condition that belongs to IBS (Figure 3B) [36-39].

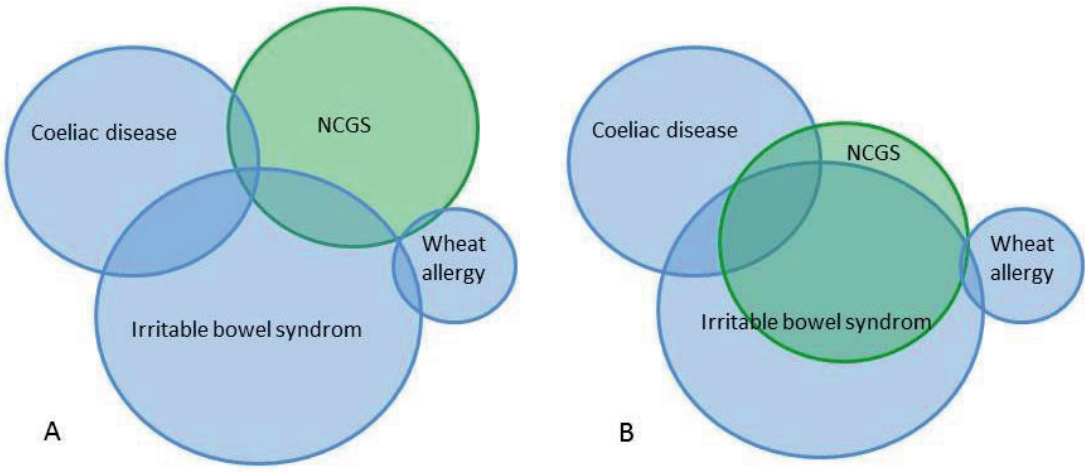

Figure 3 Overlap between gluten-related disorders. Adapted with permission from Husby et al.2015 [32]. NCGS, non-coeliac gluten-sensitivity.

1.3 Wheat structure

Wheat is among the most important food plants used for human alimentation and one of the world's major food crops, cultivated, consumed, and traded in all continents. The earliest forms of wheat were diploid einkorn (*Triticum monococcum*) and tetraploid emmer (*Triticum turgidum*). Evolution with hybridization between cultivated emmer and wild grasses has led to the currently most widely cultivated tetraploid (*Triticum durum*) and hexaploid (*Triticum aestivum*) wheat variants [40]. About 95 % of the wheat grown worldwide is the hexaploid variant because of the ability to adapt to different meteorological conditions [40]. The wheat kernel contains a fibre part called bran (14 %), the embryo or germ (3 %) and the endosperm (80 %) (Figure 4). Although the quantity and quality of starch and lipids in wheat caryopsis contribute to the derived flour characteristics, proteins are the most important components that determine the features of flours. The principal wheat proteins are albumin, globulin, glutenin and gliadin. About 85 % of the caryopsis consists of carbohydrates, of which most of it is starch and a smaller part is mono-, di- and oligosaccharides, including fructans (fructo-oligosaccharides) [40].

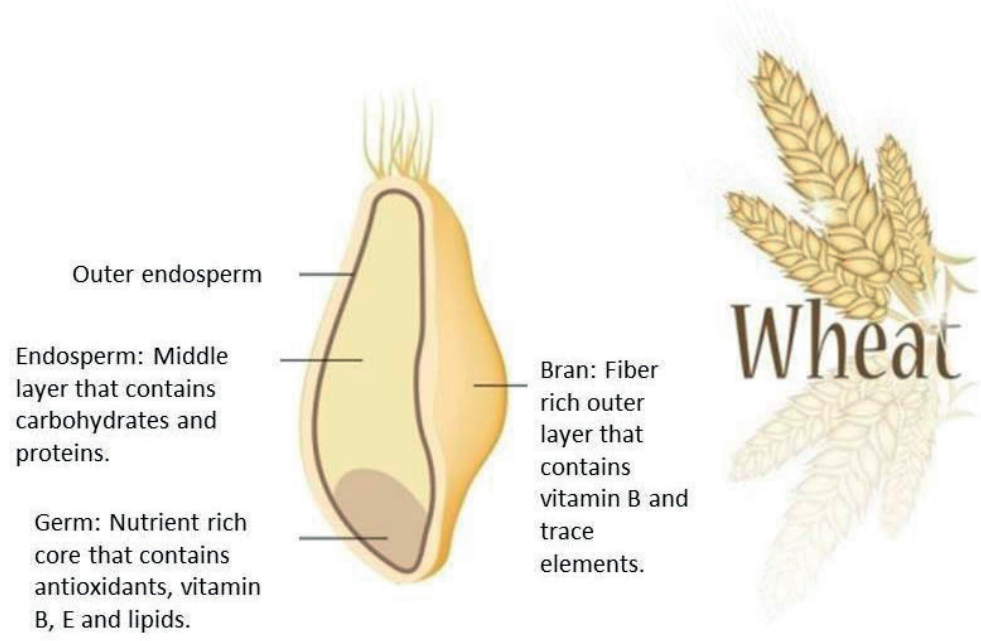

Figure 4 Structure of the wheat kernel (picture from www.photosearch.no).

Gluten

Gluten is a complex mixture of proteins, mainly gliadin and glutenin, which are referred to as prolamins [41]. Prolamins represent 80-90 % of the wheat kernel proteins. Similar storage proteins exist as secalin in rye, hordein in barley, and avenins in oats and are collectively referred to as "gluten" [41, 42]. Gluten is heat stable and is of fundamental importance for the overall appearance and textural properties of wheat-based baked products [40]. Calculations of dietary gluten intake are approximate as they are normally estimated by the amount of protein in gluten-containing cereals. The average daily gluten intake in a Western diet is thought to range from 5 to 20 g per day. In 1997 a Dutch study found a mean gluten intake in adults of 13.1 g per day [41]. Recent Danish population-based data of adults aged 20-75 years showed a mean (SD) gluten intake of 10.4 g per day (4.4) [43]. There is some evidence that modern baking practices with shortened leaving and the use of vital gluten (carbohydrate depleted wheat flour) as a food additive has resulted in increased exposure to gluten [40].

Amylase-trypsin inhibitors

Other wheat proteins include proteins associated with cell structures and enzymes. Amylase-trypsin inhibitors (ATIs) are albumin proteins acting as a natural defence of the plant and accounts for 2-4 % of the total protein in wheat. They may be involved in IgE-mediated mechanisms of wheat allergy[44]. Some of the ATIs have been reported to activate a toll-like receptor-4 dependent pathway leading to the release of pro-inflammatory cytokines in cell lines derived from coeliac and non-coeliac patients [45, 46].

Wheat germ agglutinin

Wheat germ agglutinin is a lectin, a carbohydrate binding protein found in the wheat kernel. In vitro, wheat germ agglutinin has shown epithelial damaging and immune effects. It may therefore contribute to intestinal manifestations associated with gluten intake [47].

Fructans

Fructans are subtypes of the FODMAP, the acronym for fermentable oligo-, di-, monosaccharides and polyols which are found in a variety of foods (Figure 5)[48]. Oligosaccharide fructans are polymers of fructose molecules that occur as storage carbohydrates in various plants, particularly in cereals such as wheat, rye, barley, oats and in onions, leeks, asparagus, lettuce and sunflowers [49]. These polymers are fructose residues linked to a terminal sucrose residue by glycosidic bonds, and fructans of shorter length are known as fructooligosaccharides [50]. The small intestine is not able to absorb fructans, so they continue to the colon and become fermented by the colonic bacteria [51, 52]. Since wheat is the most

important dietary source, fructans have received special interest because of the coexistence with gluten and the known capability of inducing gut symptoms [53-56].

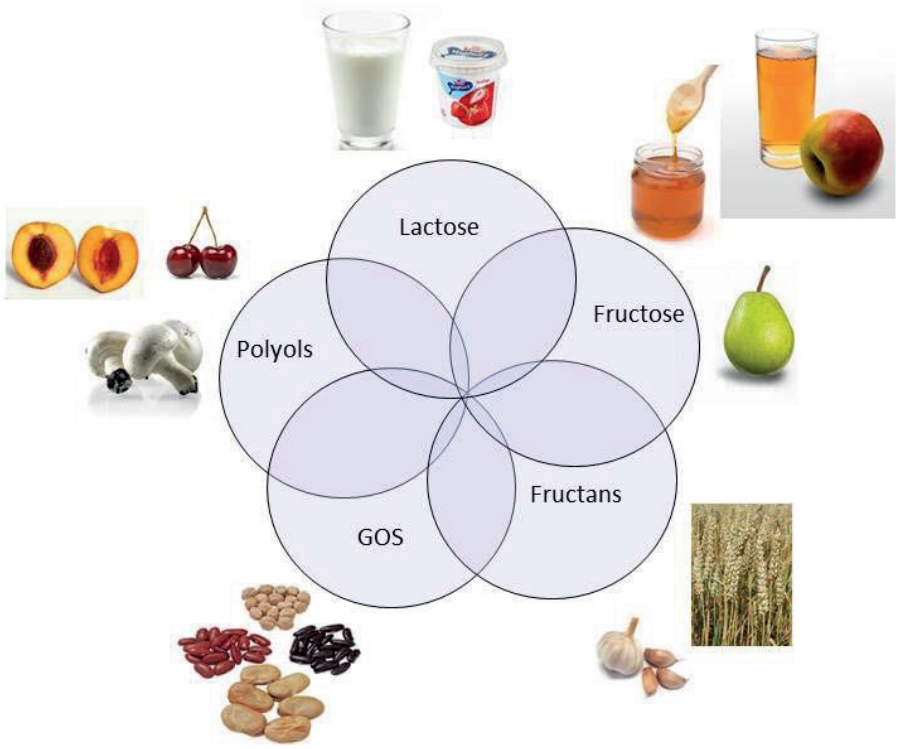

Figure 5 Sub-groups of fermentable oligo-, di-, monosaccharides and polyols (FODMAP) and examples of food sources. Overlapping circles indicate that a single food item often contains several types of FODMAP. GOS; galactooligosaccharides (adapted from Tuck CJ and Gibson PR, International Coeliac Disease Symposium, Prague, Czech Republic 2015).

1.4 Coeliac disease

Definition

In the classifications of food hypersensitivities, coeliac disease belongs to the conditions characterized with immunological reactions (Figure 1). Coeliac disease is an intestinal inflammatory disease defined as chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in individuals genetically predisposed with the human leukocyte antigen (HLA)-DQ2 and/or DQ8 genotype [22]. The gluten protein was identified as the culprit of coeliac disease by the Dutch physician, Dicke, who observed that coeliac children symptomatically improved when wheat and rye were scarce during the 1944-45 famine [57, 58].

Epidemiology

Coeliac disease is a lifelong disorder that can occur at all ages. It is an autoimmune condition that is twice more frequent in women than in men [59]. The overall prevalence in the Western population is approximately 1 % and somewhat higher in certain European countries [60]. The prevalence of coeliac disease is higher in populations at risk as in type 1 diabetes (3-6 %), first-degree coeliac relatives (up to 20 %), symptomatic (10-15 %) and asymptomatic iron deficiency anaemia (3-6 %) and osteoporosis (1-3 %)[61].

Pathophysiology

Coeliac disease arises from the interplay of genetic, environmental and immunological factors, and the pathogenesis is better understood than any other HLA-associated diseases [62]. Much of this research has been pioneered in Oslo at the Institute of Immunology, University of Oslo [63]. The disease is caused by an inappropriate immune response to dietary gluten proteins (Figure 6). Gliadin contains peptide sequences that are highly resistant to gastric, pancreatic and intestinal proteolytic digestion in the gastrointestinal tract. The reason gliadin escapes degradation is the content of the amino acids proline and glutamine, which many proteases are unable to cleave [64]. These proline-rich residues are responsible for mediating the adverse immune response [20]. This immune response is controlled by $CD4^+$ T cells in the lamina propria that recognize gluten peptides in the context of HLA-DQ2 or DQ8 molecules [20, 65-67]. The T cells are specific for proline and glutamine rich peptides in gluten that resist proteolysis. The glutamine residues become deamidated by the enzyme transglutaminase 2 (TG2). These immunological reactions result in inflammatory changes including increased intraepithelial lymphocytes (IEL), decreased enterocyte height, villous atrophy and crypt hyperplasia [20]. Whereas much of the pathogenesis of the disease now is understood, the triggering event(s) initiating the immunopathology is not well defined. Viruses that infect the intestines may certainly be prime candidates [68-70].

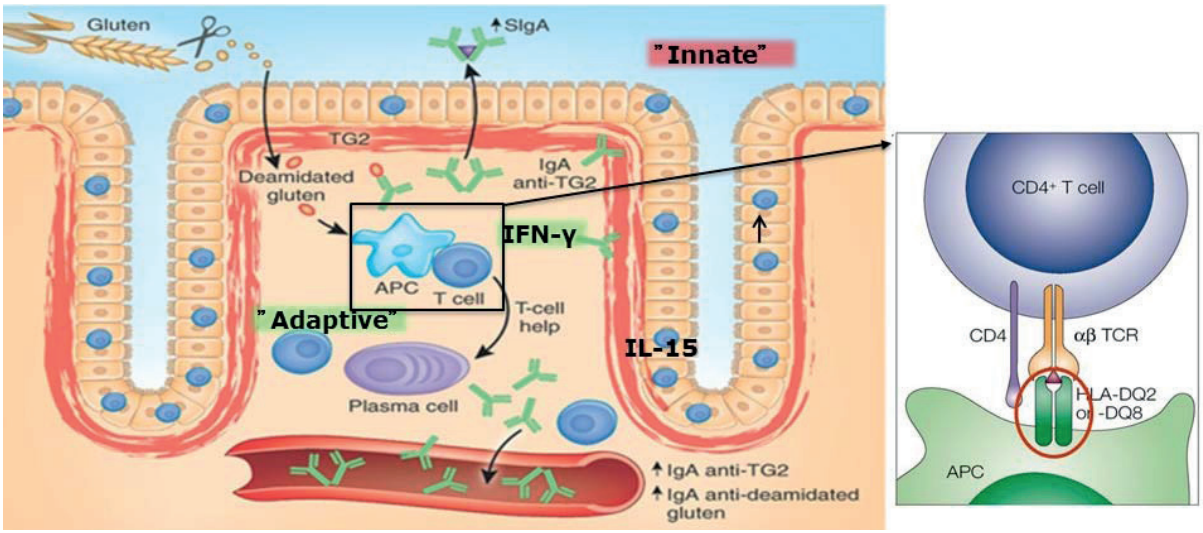

Figure 6 The inflammatory changes in the coeliac lesions (adapted with permission from Sollid & Lundin 2009) [20].

Diagnostics

The coeliac disease diagnosis depends on a combination of clinical signs, serological analysis and small intestinal morphology findings [60]. Coeliac disease can present with gastrointestinal symptoms such as diarrhoea, steatorrhea, bloating and abdominal pain, but also extra intestinal abnormalities such as abnormal liver tests, bone disease, iron deficiency and skin disorders [18]. Serology usually includes measurements of IgA antibodies to tissue transglutaminase and/or IgG antibodies to deamidated gliadin peptides. Tissue transglutaminase has 95 % specificity and is often seen with elevated endomysial and deamidated antigliadin antibodies, which are also sensitive biomarkers for detection of coeliac disease, but not specific for the diagnosis [60]. The diagnosis is confirmed by increased intraepithelial lymphocyte count, hypertrophic crypts and partial or total deterioration of villi in duodenal biopsies performed while the patient is still on a gluten containing diet [18]. Popular awareness of potential gluten-related health problems has led to increasing number of individuals pursuing self-prescribed gluten-free diet, without an adequate diagnostic workup of coeliac disease [71]. This practice poses a diagnostic challenge to clinicians, as sensitivity of available tests for diagnosis of coeliac disease reduces significantly in subjects who are not eating gluten. In such cases, recent guidelines recommend challenge with 3 g gluten daily for at least two weeks, prolonged to eight weeks if possible, followed by duodenal biopsy [18, 60, 72]. The recommendation of at least 2-week gluten challenge is based on limited evidence, and the sensitivity of this procedure is not well validated [72]. Consumption of gluten may elicit strong symptoms and patients may be reluctant to eat gluten-containing food in order to provoke diagnostic intestinal changes. This may result in a too short period of gluten exposure in order to have a reliable duodenal biopsy [73].

1.5 Irritable bowel syndrome

Definition

IBS is a chronic functional gastrointestinal disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits [74]. IBS subtypes are classified according to the 7-point Bristol Stool Form Scale and include constipation predominant, diarrhoea predominant, and IBS with predominant irregular bowel habits with a mix of diarrhoea and constipation [74, 75].

Epidemiology

Throughout the world, about 10-20 % of adults and adolescents have symptoms consistent with IBS, and most studies find a predominance females [76]. IBS symptoms come and go over time, often overlap with other functional disorders and result in a significant psychosocial burden [77]. It has been estimated that IBS is responsible for about one-third of all referrals to gastroenterology specialists and is associated with significant economic costs [78, 79].

Pathophysiology

A number of pathophysiological abnormalities have been described in IBS and include visceral hypersensitivity [80, 81], motility changes [82], infectious gastroenteritis [83, 84], intestinal inflammation (ref), altered microbiota [85-87] and psychosocial factors [88]. However, IBS is also associated with food intolerances, and approximately 84 % of patients report that symptoms are related to certain food items [89, 90]. Studies have found that IBS patients may respond to elimination diets [91, 92]. Exclusion diet-rechallenge methodologies applied to patients with IBS have identified foods comprising large content of wheat and other grains as frequent culprits in inducing symptoms [53, 93, 94]. Abdominal symptoms have been specifically induced following challenges with oligosaccharides [95-99].

Diagnostics

In absence of objective biomarkers and alarm symptoms, an important part of the diagnosis of IBS is the exclusion of other possible diseases. Further, the Rome Foundation has developed clinical guidelines for the diagnostics of IBS, last updated to the Rome IV criteria in 2016 [74]. The assessment includes history of symptoms regarding onset, duration and frequency. Symptoms and stool patterns are further described and bowel habits categorised by the Bristol Stool Form [75]. In this thesis subjects with IBS were defined by the Rome III criteria as shown in Table 2 [100].

Table 2 Rome III Criteria for irritable bowel syndrome

Characteristic	Rome III
Diagnostic time frame	Symptom onset at least six months prior Symptom activity during the last three months Symptom frequency the last three months
Symptom description	Abdominal discomfort and pain
Symptom association	Improvement with defecation Onset associated with change in the form of stool Onset associated with the change in the frequency of stool
Predominant stool pattern of IBS subtype	Stool type based on bowel movements on all days
Tool to categorise bowel habit	Bristol Stool Form Scale

IBS; irritable bowel syndrome.

Management

Management of IBS include lifestyle and dietary modifications, psychological and behavioural treatments and different types of medication such as opioid agonists, antidepressants, antispasmodics, probiotics and antibiotics [74, 101-103]. However, in recent years, the dietary approach has received increased attention, and many studies have found effect of dietary guidance on symptoms and quality of life in IBS patients [104-106].

Approximately 80 % of patients with IBS report food intolerances [7] and studies have claimed that IBS patients may benefit from a gluten-free diet, in particular the diarrhoea predominant subtype [107-110]. The clinical and scientific community has been quick to point to gluten as the pathogenic molecule. Vazquez-Roque et al suggested that effect of gluten-free diet on symptoms and bowel barrier functions in IBS-D was attributed to the removal of gluten [110], and Shahzbazkhani et al. claimed that many patients diagnosed with IBS were gluten sensitive and that their symptoms could be controlled with a gluten-free diet [109].

1.6 Non-coeliac gluten sensitivity (NCGS)

Definition

In 2012 Lundin and Alaedini suggested to define NCGS as a condition "associated with the experiencing of various symptoms in response to ingestion of foods containing wheat, rye and barley, and the resolution of symptoms on removal of those foods from diet in individuals in whom coeliac disease and wheat allergy have been ruled out" [22, 111].

The first descriptions of gluten sensitivity in absence of coeliac disease were done in England in 1976 [112]. The researchers performed a challenge study of eight women with dramatic relief of symptoms as response to gluten-free diet, and without evidence of coeliac disease. Further, they found significant worsening of abdominal pain and diarrhoea in response to four-week gluten exposure [112]. However, this gluten challenge is poorly described. The phenomenon has been "rediscovered" in recent years and described by Verdu et al. as the "no man's land" between IBS and coeliac disease [113], and several review articles and editorials have been published [33, 38, 114-118]. Biesiekierski et al. demonstrated in a double-blind randomised placebo-controlled trial that gluten caused gastrointestinal symptoms in subjects without coeliac disease. The study was sited in support of the existence of NCGS [107]. However, a follow-up study was not able to reproduce the findings [119]. It is continuously discussed whether NCGS is a separate entity from "ordinary" IBS with food (gluten) dependent symptoms [36, 54, 120].

Epidemiology

Accurate figures of NCGS prevalence do not exist due to the lack of well-defined objectively verifiable diagnostic criteria. Estimates are therefore given as the proportion of people who self-report gluten or wheat sensitivity or the proportion of people on gluten-free diet without having coeliac disease. The figures range from 0.6 % to 13 % ([34 23, 24, 121-127]). In the USA the prevalence of people without coeliac disease who avoid gluten increased from 0.5 % in 2009 to 1.7 in 2014 [71]. The prevalence of gluten-free diet is higher among women than among men [23]. Recent Italian estimates from a teenage cohort of 555 students were that1 % had established coeliac disease, 12 % reported NCGS and 3 % followed a gluten-free diet. Only 23 % of the self-reported NCGS had consulted a doctor and 14 % had undergone serological tests for coeliac disease [128]. Most of the self-reported NCGS presented with IBS-symptoms (44 %). The condition is also described in children with uncertain prevalence figures [129, 130].

Pathophysiology

The pathophysiology of NCGS is unclear, and the wheat components that are responsible for the development of symptoms have not been clearly defined. Table 3 presents the different biomarkers used to diagnose coeliac disease and how the same markers are unreliable for NCGS. Possible mechanisms have included innate and adaptive immune activation, impaired intestinal epithelial barrier and changes in microbiome. Negative serology for specific antibodies and lack of association with HLA-DQ2/DQ8 suggest a limited involvement of adaptive immune mechanisms in NCGS [131]. A higher expression of toll-like receptors in intestinal mucosa as compared to coeliac disease patients, have indicated a stronger role of innate immune mechanisms in NCGS [131]. Experimental studies have repeatedly shown increased IEL changes in intestinal permeability and some cytokine response after gluten challenge, but all findings have to date been considered unreliable as diagnostic biomarkers [131-133].

Table 3 Gluten sensitivity tests

Diagnostic tools	Coeliac disease	Non-coeliac gluten sensitivity
Coeliac disease serology		
Anti-tissue transglutaminase	Positive	Positive/negative
Anti-gliadin antibodies	Positive	Positive/negative
Anti-endomysial antibodies	Positive	Negative
Anti-deamidated gliadin peptide antibodies	Positive	Negative
Duodenal histology	Positive (Marsh 2-3)	Negative (Marsh 0-1)
HLA-DQ2/DQ8	Present	Absent/present
IgE-based assays	Negative	Negative
Clinical features	Troubles caused by ingestion of wheat and their disappearance on gluten-free diet	Troubles caused by ingestion of wheat and their disappearance on wheat/gluten-free diet

Table 4 summarises some of the findings related to suggested possible mechanisms in the pathogenesis of NCGS. Increased intestinal permeability in NCGS as compared with healthy controls has been reported by several research groups [131, 134]. Hollon et al demonstrated greater increase in intestinal permeability in NCGS and coeliac disease after gliadin exposure than in coeliac disease remission [134]. According to Sapone et al the expression of the innate immunity marker Toll-like receptor 2 was increased in NCGS as compared to coeliac disease, and expression of a T-regulatory cell marker was significantly reduced in NCGS relative to controls and coeliac disease individuals [131]. The authors suggest an important role of the innate immune system without any involvement of the adaptive immune response. Di Sabatino et al. investigated innate and adaptive immunity in self-reported NCGS versus coeliac disease and found no abnormal mucosal immune response in individuals with NCGS [135]. A Norwegian study comparing coeliac disease and NCGS with healthy

controls in an open gluten challenge found increased density of IELs before challenge and a significant increase in m-RNA for interferon-γ after challenge in the NCGS subjects [132].

Table 4 Observations of biochemical and physiological features in NCGS and IBS

Author	Observed change	Suggested dietary culprit
Gibson et al. 2012 [136]	Increased water delivery and fermentable substrates to the colon	FODMAP
Sapone et al. 2011 [131]	Increased claudine 4	Gluten
Brottveit et al. 2013 [132]	Increased interferon-γ m-RNA Increased IEL compared to healthy controls	Gluten
Volta et al. 2011[137]	Antigliadin antibodies IgG	Gluten
Hollon et al. 2015 [134]	Increased intestinal permeability	Gluten
Schuppan et al. 2015 [46]	Stimulation of innate immune cells	ATI

m-RNA; messenger-ribonucleic acid, IEL; intraepithelial lymphocytes, FODMAP; fermentable oligo-, di-, monosaccharides and polyols, ATI; α-amylase trypsin inhibitor

Diagnostics

A subject with suspected NCGS may present with either or both gastrointestinal and extra intestinal symptoms similar to coeliac disease. The investigation starts with adequately exclusion of coeliac disease, as shown in Figure 7, preferably before any dietary changes have been done [133, 138]. However, many individuals with self-reported gluten sensitivity have started gluten-free diet without proper examinations. In such cases, HLA-DQ2/DQ8 positive individuals predisposed to coeliac disease should be subjected to a gluten challenge followed by a gastroscopy. An adequate amount of dietary gluten exposure is required to have a reliable duodenal biopsy. A daily intake of four slices of bread for four weeks induce diagnostic changes in duodenal biopsy [18]. The duration of the challenge is a compromise of the 2-8 weeks suggested in the guidelines. However, reluctance to gluten challenge because of a fear of relapse of symptoms often hampers the investigation of coeliac disease. The result is individuals on gluten-free diet with unsettled diagnosis. If, however, the exclusion of coeliac disease is made by either negative HLA-DQ2/DQ8 and/or negative duodenal biopsy while on a sufficient amount of dietary gluten, the workup continues in a collaboration between a dietitian and a gastroenterologist. It includes a thorough diet and symptom history to exclude non-gluten triggers, and continues with a standardised gluten challenge and symptom recording. This is a purely clinical approach based on symptom generation as response to a standardised open or blinded challenge. In 2015, a panel of clinicians and researchers published a non-scientific recommendation on how NCGS should be diagnosed. It included a standardised DBPCFC and ≥30% change of symptoms as response to the gluten challenge [139].

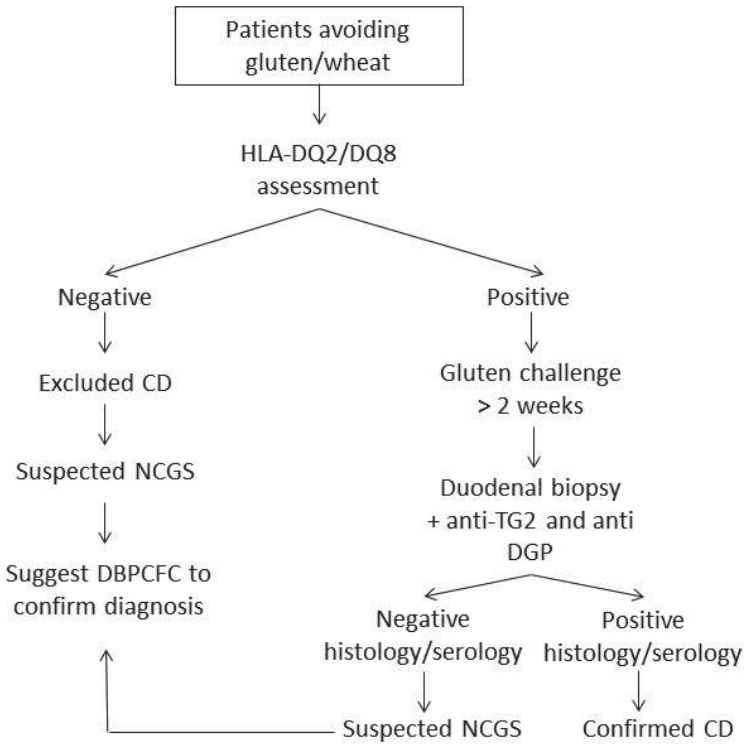

Figure 7 Suggested algorithm for the workup of non-coeliac gluten sensitivity (NCGS) adapted from Volta 2017[133]. HLA; human leukocyte antigen, DBPCFC; double-blind placebo-controlled food challenge, TG2; anti-tissue transglutaminase 2, DGP; deamidated gliadin-peptide.

Dietary management

Gluten-free diet has been adopted by individuals with self-reported NCGS, and some studies have described how the diet is applied by this population [127, 140, 141]. Tavakkoli et al. observed that 50 % of NCGS on gluten-free diet avoided additional food [141]. Zingone et al. identified that fruit, vegetables, milk and dairy products were frequently avoided foods in addition to the gluten exclusion [140]. A Dutch study found that 74 % of NCGS patients on gluten-free diet reported abdominal discomfort related to at least one high FODMAP containing food as compared to 22 % of the controls [127]. Studies of the nutritional quality of gluten-free diet in NCGS have found lower intake of protein, fiber and polyunsaturated fatty acids in NCGS patients as compared to healthy controls [140]. No studies have until now described how a non-coeliac group complies to the gluten-free diet as compared to individuals with coeliac disease.

1.7 Gluten-free diet

The only current treatment option for coeliac disease is strict, lifelong gluten-free diet, which usually results in mucosal healing [60, 142]. The treatment also aims to correct immunological abnormalities, minimize symptoms and reverse protein-energy deficiency and abnormal bone health [143]. With adherence to the gluten-free diet the therapeutic goals can be achieved in almost all patients with coeliac disease within five years after diagnosis [143].

As soon as the coeliac disease diagnosis is confirmed, a referral to a coeliac disease-trained dietitian for education in gluten-free diet is recommended [144-146]. First, the dietitian educates in how to keep the diet free from gluten. Second, the focus is how to keep food diversity and nutritional value in a restricted diet. Addressed issues are balanced meal planning, fibres and enrichments, hidden gluten sources and label reading [117].

Gluten-free diet is based on the elimination of the alcohol-soluble protein fractions of gliadin in wheat, secalin in rye and hordein in barley, that are all toxic in coeliac disease. The cereals are replaced by gluten-free cereals such as rice, corn, buckwheat and millet. Moreover, some leguminosae such as quinoa, amaranth and soybean are particularly useful due to their high protein content quality as replacements for their gluten containing analogues [147]. Oats that are not contaminated with wheat (after a dedicated supply chain and manufacturing) have shown to be safe in a gluten-free diet in coeliac disease and are both allowed and recommended as part of gluten-free diet in most countries [148-150]. A diet mainly based on naturally gluten free cereals and non-processed food (meat, fish, poultry, egg, fruit and vegetables) facilitate gluten-free diet adherence and secure the nutritional value of the diet.

However, any restrictive diet is at risk of nutritional inadequacy. Previous studies have generally but not always found the gluten-free diet to be nutritionally inadequate [151-153]. Some deficiencies are related to habitual poor food choices, and some to inherent deficiencies of gluten-free diet. A study of Australian coeliac disease patients found that inadequacies of folate, calcium, iron and zinc were more frequent than in the general population [154]. Gluten-free diet may have negative social, financial and health consequences, and some authors have advised against a life-long diet for individuals without coeliac disease [155].

1.8 Diet low in FODMAP

A diet low in FODMAP has shown to be a successful approach in the management of symptoms in IBS [98, 156-158]. It was first suggested as a new approach to Crohns Disease in Australia about 12 years ago and is now an internationally accepted dietary strategy for IBS [159, 160]. The dietary management is a dietitian-driven education process containing 6-8 weeks where foods rich in FODMAP are restricted (Figure 8). The elimination phase is followed by a standardised reintroduction phase [158].

FODMAP have small molecular size that exerts an intestinal osmotic effect leading to increased delivery of water to the colon [53, 161]. In the colon, fermentation of the short-chain fermentable carbohydrates results in the production of short-chain fatty acids such as acetate, propionate and butyrate, and gases such as carbon dioxide and methane [136, 162]. These by-products contribute to growth and functioning of the gut microbiota [12, 163]. In susceptible individuals, distension of distal small and proximal large bowels by rapid gas production and the additional fluid load may induce gastrointestinal symptoms such as pain, bloating and altered bowel habit [136]. Studies of various designs have found efficacy of FODMAP reduction in about 70 % of patients with IBS of any category [105, 156, 157, 164-166]. The concept is now implemented as a treatment option in the up-dated guidelines from National Institute for Health and Clinical Excellence [103].

Figure 8 FODMAP exist in a variety of foods (Photo: Øystein H. Horgmo, University of Oslo). FODMAP; fermentable oligo-, di-and monosaccharides and polyols.

1.9 Knowledge gaps

Symptom relief and health benefits have motivated non-coeliac people to institute a gluten-free diet. Patients with coeliac disease are educated in strict diet adherence. However, little is known about diet adherence in non-coeliac patients that are mostly self-instituted on the gluten-free diet. Further, the gluten exposure during gluten-free diet has never been estimated in this patient group.

In 2009-2015 Oslo University Hospital used a standardised open bread challenge to assess NCGS in a clinical setting. The classification of NCGS or non-NCGS was performed by a gastroenterologist based on clinical interview and symptoms scores, but without any predefined standard for symptoms change. For the first time, standardised cut-offs for symptom change in investigation of NCGS were published by a panel of researchers and clinicians in 2015. These standards have never been applied to the Norwegian patient material, or any other patient group.

Proper exclusion of coeliac disease is crucial in the clinical investigation of NCGS. A major problem with the assessment of NCGS is that self-reported gluten-sensitive subjects often institute a gluten-free diet without adequate workup for coeliac disease. If symptom relief has been achieved in response to the gluten-free diet, subjects may be reluctant to gluten exposure for diagnostic purpose. To overcome this problem, recent guidelines suggested gluten exposure of two weeks as a minimum, and up to eight weeks in order to have a reliable duodenal biopsy [18]. However, the minimum of two weeks of gluten exposure before gastroscopy has not been well validated [72].

The culprit of symptoms in NCGS is not clearly defined. Thus, the pathogenesis remains unclear. Some studies have found increase of symptoms in response to gluten challenge, and symptom relief in response to gluten removal. However, alteration of the gluten content of the diet has effects on dietary constituents in addition to gluten. The studies have failed to show that symptom improvement has been due to the gluten removal per se, and overlooked the presence of other components with proven pathogenic capabilities, such as the poorly absorbed FODMAP and in particular the wheat fructans. Fructan challenge has never been done in self-reported gluten sensitive subjects without coeliac disease.

2 AIMS

The overall aim was to study gluten-free diet in NCGS, evaluate diagnostic methods in coeliac disease and NCGS and to study symptom triggers in NCGS. The specific aims of the papers were as follows:

Paper I

To assess and compare diet adherence and gluten exposure in subjects with coeliac disease and subjects with self-reported NCGS.

Paper II

To compare the results of an open bread challenge in patients suspected of having NCGS in the period 2009-2015 with recently suggested definitions of symptom change.

Paper III

To investigate whether a 14-day gluten challenge is enough to invoke villous blunting in well-treated subjects with coeliac disease, and to study whether the diagnostic sensitivity of a short gluten challenge can be improved by applying other methods and biomarkers.

Paper IV

To investigate the effect of gluten and fructans separately by a randomised double-blind placebo-controlled crossover challenge in subjects with self-reported gluten sensitivity and in whom coeliac disease and wheat allergy were adequately excluded.

3 METHODS

3.1 Design and participation

Table 5 shows an overview of the samples and the types of studies in the four papers. The following sections will describe the study sample and study design of each of the papers.

Table 5 Overview of study samples and designs in papers I-IV

Paper	Subjects	n	Type of study	Recruitment
I	Coeliac disease NCGS	23 34	Cross-sectional	Oslo University Hospital: patient referrals Norwegian Coeliac Society: advertisements Newspaper advertisements
II	NCGS	56	Cross-sectional	Oslo University Hospital: patient referrals
III	Coeliac disease	19	Uncontrolled intervention	Oslo University Hospital: advertisements and patient referrals Norwegian Coeliac Society, Facebook: advertisements
IV	NCGS	59	Randomised clinical trial	

NCGS, non-coeliac gluten sensitivity

3.1.1 Paper I

The data of paper I was obtained from a previous study consisting of subjects with confirmed coeliac disease and subjects with self-reported gluten sensitivity, aged 17-65 years and recruited in the period 2009-2010. Participant flow is described in detail elsewhere [167]. The self-reported gluten sensitive subjects had not previously been properly investigated for coeliac disease. During the follow up three of these were diagnosed with coeliac disease [167]. However, in paper I this gluten sensitive cohort is referred to as NCGS subjects. One coeliac disease subject and one NCGS subject were reluctant to be interviewed about their diet. Thus, 23 coeliac disease subjects and 34 NCGS subjects were included in the study.

3.1.2 Paper II

Open bread challenge

The open bread challenge described in paper II was a clinical tool for the investigation of patients suspected of having NCGS referred to Oslo University Hospital in the period 2009-2015, a collaboration between Department of Gastroenterology and Division of Clinical Nutrition (Figure 9). A dietitian carried out nutrition assessment and a standardised dietary history. Patients then underwent a 3-14 days open challenge of four slices of white bread (120 g) per day. Symptom recordings were returned to the dietitian who calculated symptom scores. The gastroenterologist evaluated the individual challenge response and concluded positive or negative diagnosis of NCGS, without any predefined cut-off for symptom change. The diagnosis was used by the patients when they applied for reimbursement for gluten-free food (as defined by National Administration of Labour and Welfare) [168].

The bread was purely wheat based and patients were instructed to buy a certain brand of sandwich bread from the food store (Sandwhich bread or Paagen Sandwhich). Retrospective analysis showed that 100 grams of white bread contained 6.8 g of gluten and 2.1 g of fructans.

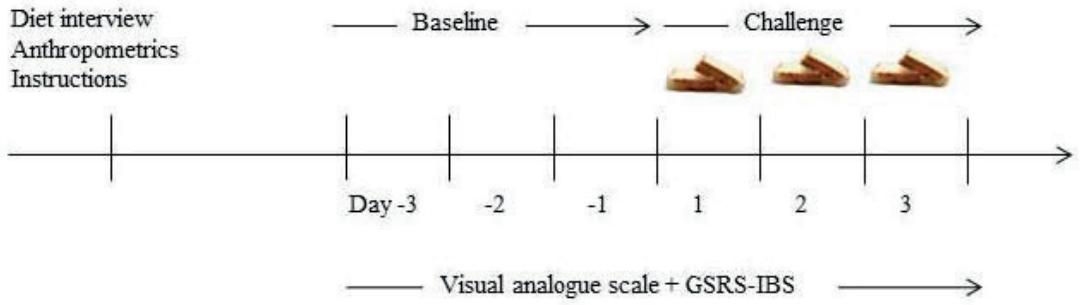

Figure 9 Outline of open bread challenge of paper II.

Study sample paper II

The study sample of paper II were subjects aged 17-75 years that had been referred to the Oslo University Hospital, Department of Gastroenterology's outpatient clinic with suspicion of NCGS. The subjects underwent an open bread challenge in the period 2009-2015. Dietitian's and clinician's reports were analysed from medical records composing a retrospective quality control study. The subject flow is given in Figure 10.

The subjects were self-instituted on gluten-free diet followed by self-reported symptom relief. Coeliac disease was considered ruled out if clinical history showed normal duodenal biopsy while on a gluten-containing diet, or if the coeliac disease compatible genotypes HLA-DQ2.5 or –DQ8 were negative. Subjects with clinically defined wheat allergy were considered not suitable for challenge.

Of 63 subjects referred for NCGS in the given period, 56 (44 women) completed the open bread challenge protocol with either GSRS-IBS or VAS recordings. Both measures were recorded in 42 subjects.

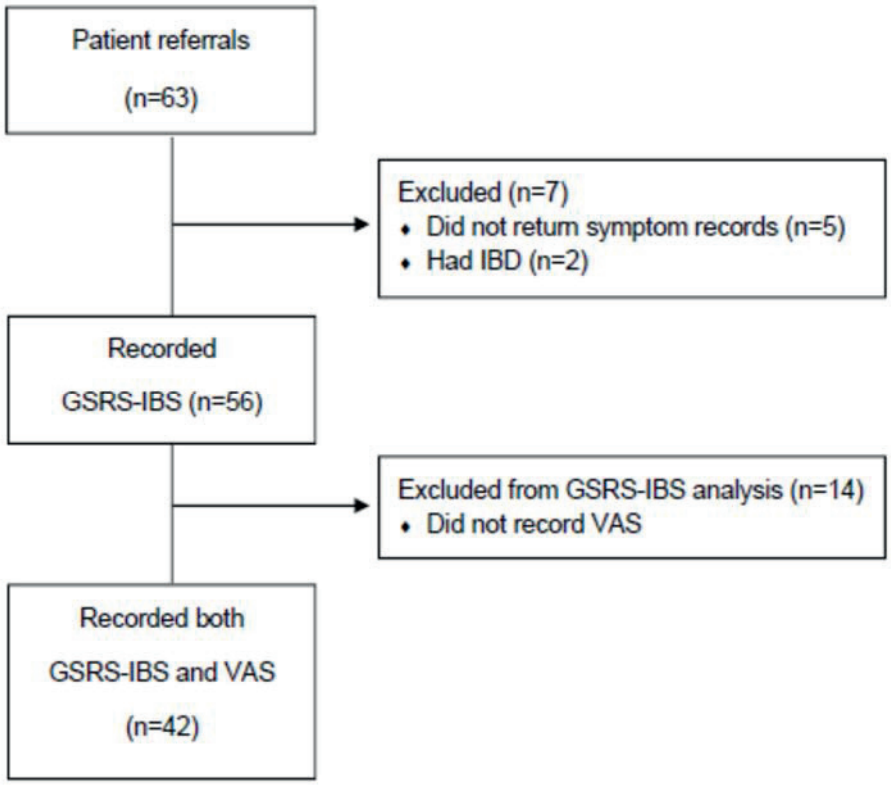

Figure 10 Flowchart of subjects in paper II. GSRS-IBS, Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome version, VAS, visual analogue scale.

3.1.3 Paper III

Open gluten challenge

Figure 11 shows the time line of the open 14 days gluten challenge of coeliac disease subjects of paper III. The subjects ingested a muesli bar containing 5.7 g of gluten once daily (Figure 12). The same gluten muesli bar was used in the challenge of the NCGS subjects in paper III. Apart from the gluten-containing muesli bar, the subjects continued their regular gluten-free diet. They underwent the first day of gluten challenge under medical supervision.

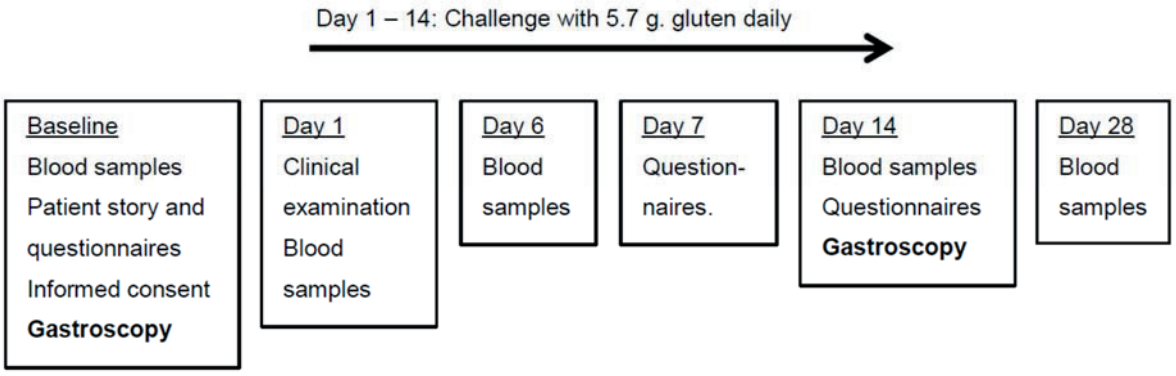

Figure 11 Outline of the challenge study of paper III.

Figure 12 Quinoa-based muesli bar as challenge vehicle in the study of paper III and IV.

Study sample of paper III

Figure 13 shows how 78 subjects aged 18-80 years were screened according to the following criteria in the study of paper III:

Inclusion criteria:

- Coeliac disease verified by either positive biopsy or positive serology before start of gluten-free diet if biopsy is yet not done and is expected to be positive after a challenge.
- Strict adherence to gluten-free diet for at least the last six months.

Exclusion criteria:

- Pregnancy or lactation.
- Women of fertile age not taking adequate contraceptive measures.
- Use of immunosuppressive medication for the last three months.
- Chronic or severe acute infection.
- Allergy to sesame seeds, pecan or macadamia nuts.
- Positive anti-transglutaminase 2 IgA or duodenal biopsy (Marsh 2 or 3) at baseline.

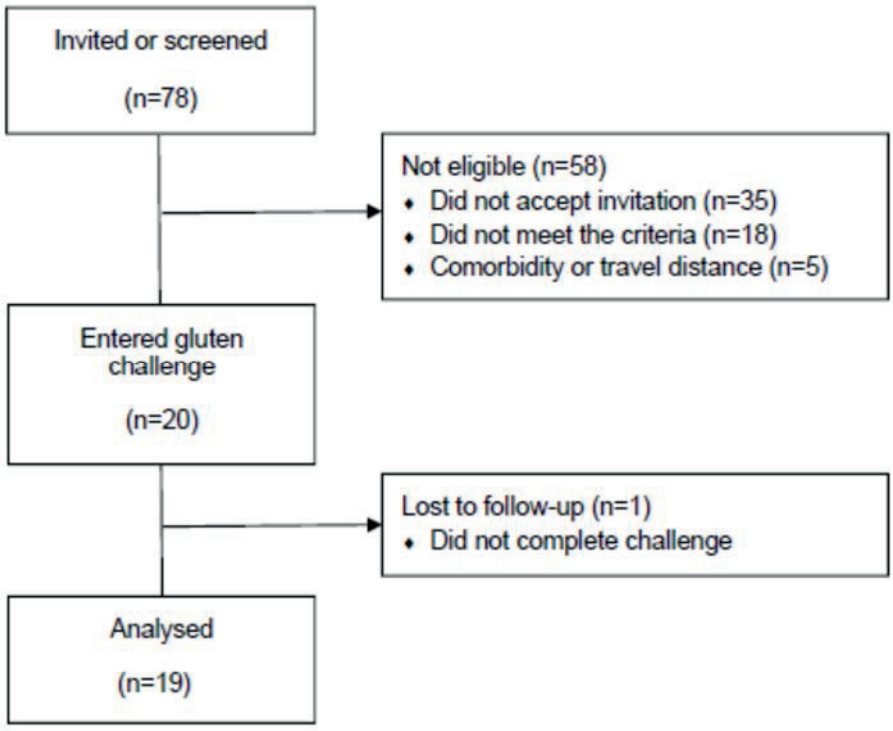

Figure 13 Flowchart of subjects in paper III.

3.1.4 Paper IV

Blinded gluten and fructan challenge

The study of paper IV was a randomised clinical trial (RCT). Figure 14 shows the design of the randomised, double-blind, placebo-controlled, crossover study with three periods and six sequences (ABC/ACB/BAC/BCA/CAB/CBA). Each challenge appeared the same number of times within each period and sequence. Further, the crossover design was balanced so that each challenge preceded every other challenge the same number of times.

Baseline information was obtained in an interview based on a standardised clinical report form (Appendice). Baseline diet and symptoms were recorded during a seven-day period before start of challenge. They were then randomised to one of the six sequences of the seven-day challenges by gluten, fructan and placebo, followed by a minimum of one-week washout period. Washout periods were extended until the symptoms from previous challenge were resolved. All subjects and study team members were blinded throughout the study. Details of randomisation and blinding are described in paper IV.

The challenge vehicle was a quinoa-based 50 g, 220 kcal low-FODMAP gluten-free muesli bar that was eaten once daily (Figure 12). The muesli bars were developed and produced by the Monash University, Australia. They were balanced in carbohydrates, fibre, fat and protein and had similar appearance, texture and taste. The fructan bar was added 2.1 g of fructo oligosaccharides (Orafti® Oligofructose) and the gluten bar 5.7 g of gluten. The gluten was commercially available, carbohydrate depleted wheat gluten (Vital Wheat Gluten, Manildra Group, Gladesville, New South Wales, Australia).

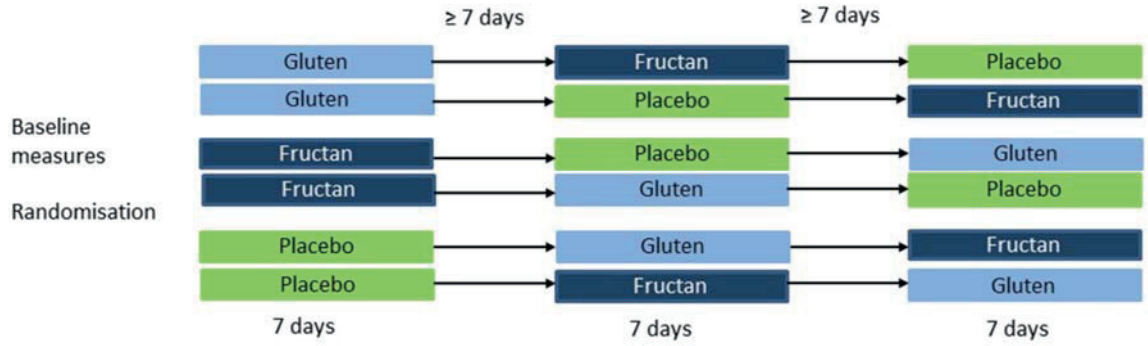

Figure 14 Crossover design of the study in paper IV.

Study sample of paper IV

The subjects of paper IV were adults aged 18-80 years with self-reported gluten sensitivity recruited to a randomised clinical trial at Oslo University Hospital from October 2014 to May 2016 according to the following inclusion criteria:

- Strict adherence to gluten-free diet for at least the last six months.
- Reported and measured symptom relief of gluten-free diet.
- Coeliac disease excluded by normal duodenal biopsy while on gluten-containing diet or absence of the genotype HLA-DQ2/8.
- Wheat allergy excluded by negative wheat specific IgE.

Exclusion criteria were:

- Pregnancy or lactation.
- Use of immunosuppressive medication for the last three months.
- IBD or other comorbidity.
- Chronic or severe acute infection.
- Women of fertile age not taking adequate contraceptive measures.
- Allergy to sesame seeds, pecan or macadamia nuts.

Of 232 subjects assessed, 68 were found eligible (Figure 15). Of the excluded, 111 subjects did not meet the inclusion criteria: coeliac disease properly excluded (n=61), long travel distance (n=20), not gluten-free (n=21) or symptomatic on gluten-free diet (n=4). Two subjects were excess according to the predefined 66 subjects needed, thus two extra sequences were made by an external dietitian and kept double blinded. The subjects chose to proceed from baseline and completed the protocol, but were told from the start that they would be excluded from the statistical analysis. Three more subjects were excluded from analysis because of late discovery of coeliac disease related finding of the baseline measures. One had duodenal biopsy of Marsh 3 despite gluten-free diet and former negative biopsy on gluten containing diet. Two had positive HLA-DQ2/8 genotype in blood tests without any further exclusion of coeliac disease. The remaining 59 subjects completed all three challenges and were included in the analysis.

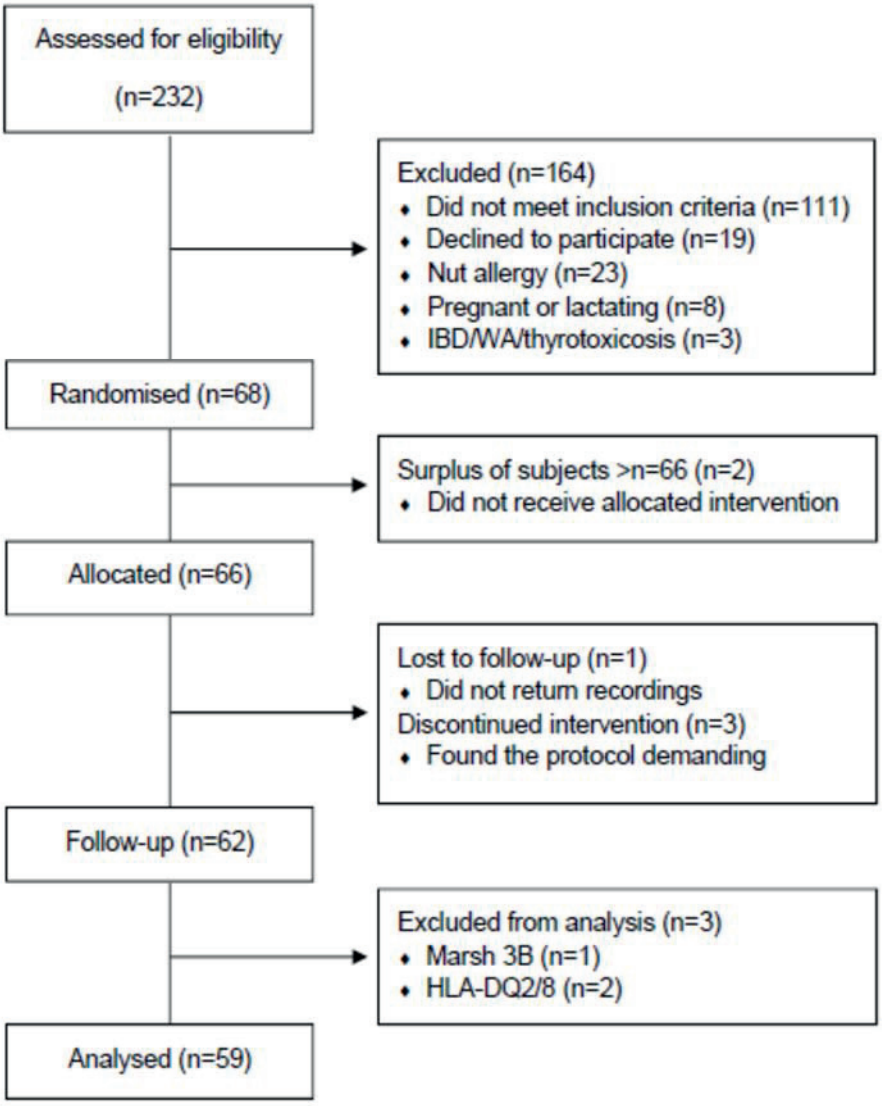

Figure 15 Flowchart of subjects in paper IV. IBD, inflammatory bowel disease, WA, wheat allergy, HLA, human leukocyte antigen

3.2 Dietary assessment

Dietary assessment was performed in paper I and IV. After thorough instruction, subjects were asked to record their food intake by a three-day weighed food record (paper I) and by seven-day dietary record (paper IV), (Table 6). They were told to maintain their usual gluten-free diet and to record recipes and the names of all products consumed.

In paper I underreporting of food intake was assessed by calculated energy intake and calculated basal metabolic rate (BMR). A BMR-factor (energy intake/BMR-ratio) less than 1.47 was considered as underreported food intake [169].

In paper IV, sources of FODMAP were extracted from the seven-day dietary record and the intake of fructans and total FODMAP was calculated using the nutrition software Foodworks, Version 7 (Xyris Software Australia Pty Ltd, Highgate Hill, QLD, Australia).

Table 6 Dietary assessment methods used in the thesis

	Record by weighing Paper I	Record by household measures Paper IV
Description	All food and beverages consumed weighed and recorded	All food and beverages consumed recorded by household measures
Duration	3 consecutive days including Saturday or Sunday	7 consecutive days
Equipment	Household scale	Picture booklet of portion sizes

3.3 Gluten-free diet adherence

In paper I adherence to gluten-free diet was assessed by interviewing the subjects about their meal situation, and their use of gluten-free and naturally gluten-free products, by means of a frequency questionnaire and additional standardised questions related to diet understanding and diet practice. The dietitian then categorized the adherence into one of four categories given in Table 7. Reported intakes of regular food used less frequently than once a month, were not included in the calculations of gluten exposure. Energy intake was calculated by means of the Norwegian Food Composition Table (www.matvaretabellen.no).

In paper IV, diet adherence was measured by using a locally developed and unpublished self-administered questionnaire based on information from focus groups and the coeliac disease adherence

test (CDAT) (Appendice) [170]. The questionnaire contained eleven questions with a Likert scale of 1-5 where lower scores indicated good adherence.

Table 7 Categories of adherence to gluten-free diet

Good	Intake of always known gluten-free food at home and away from home, always checking of labels, no voluntary transgression
Fair	Possible risks like less checking of ingredients, no asking for ingredients in menus when eating out
Poor	Additional obvious risks like consuming food of unknown composition, tasting of gluten containing food or having regular beer weekly or more frequently
Non-adherent	Eating regular meals in certain periods, occasions (i.e.vacations, celebrations)

3.4 Prolamin and fructan analyses

In paper I, a substantial sampling of selected gluten-free and gluten-containing foods was done from regular food markets and special food stores in central parts of Oslo. The samples were analysed by the sandwich R5-ELISA Ridascreen® Gliadin competitive method (Art. No.R7011 and Art. No.R7021). Non-detectable concentrations were set at less than 5 mg gluten/kg. The mean of the duplicate gluten values was applied for the calculations of gluten exposure.

The muesli bars used in the study of paper III and IV were analysed with the same method to confirm the presence and amount of gluten in the gluten containing muesli bar, and absence of it in the fructan and placebo bar. Further, the presence of 33-mer peptides in the gluten containing muesli bar and their absence in the placebo muesli bar were confirmed by mass spectrometry and label free quantification (The Proteomics Core Facility, Department of Immunology and Transfusion Medicine, Oslo University Hospital, Oslo, Norway).

The content of fructans in the muesli bar was set to mimic the amount of fructans in four slices of white bread, as used in the open challenge of paper I. White bread were sampled, extracted and freeze-dried according to a standardised sampling procedure [49]. The samples were sent to the Monash University and analysed by the Megazyme Fructan HK kit and high performance liquid chromatography [55].

3.5 Coeliac disease morphology and serology

In the study of paper III gastroduodenoscopy was done at baseline and repeated on day 14 of gluten challenge in the coeliac subjects. Mucosal remission status at baseline was initially determined by non-blinded routine biopsy assessment. An experienced gastrointestinal pathologist performed the morphometric measurements, cell counting and establishment of Marsh scores, blinded for participant identity and study visit [171]. Mean villous height by crypt depth ratio and quantification of IEL was performed. An IEL-count of 25 per 100 enterocytes was used as cut-off between Marsh scores 0 and 1[63].

Measurement of anti-TG2-IgA and anti-DGP-IgG was done at baseline and repeated in the coeliac subjects on day 6, 14 and 28 after start of challenge. Gluten-specific T-cells binding to HLA-DQ:gluten tetramers were analysed by flow cytometry at baseline and on day 6 of gluten challenge in the coeliac subjects.

3.6 Patient reported outcome measures

Recording of symptoms was performed in paper II-IV. Gastrointestinal symptoms were the primary outcome measure in paper II. In paper IV the subjects recorded both gastro- and extra intestinal symptoms. In all the studies self-administered questionnaires were used. The selection of symptoms and questionnaires reflected the clinical characteristics of NCGS described in the literature [121, 122, 172] and which methods that were already applied for similar patients in clinical and scientific settings at Oslo University Hospital [132, 173]. In paper III a coeliac disease specific questionnaire was used [174]. Table 8 presents an overview of the patient reported outcome measures.

Visual analogue scale (VAS)

In paper II-IV gastrointestinal symptoms were additionally measured daily using a 100 mm visual analogue scale (VAS). The method is widely used to record subjective symptoms in challenge studies of IBS and NCGS [107, 119] and in clinical and scientific investigation of food allergies and intolerances (Appendices) [175, 176]. VAS was used to measure abdominal pain, bloating, passage of wind, nausea, stool dissatisfaction and overall symptoms (papers II-IV). Further, extra intestinal symptoms often reported in NCGS literature; numbness and tingling in hands and feet, concentration problems and pain in joints and muscles were recorded by VAS (Table 8) [24, 111, 122]. Finally, the six fatigue complaints were also recorded using VAS.

Table 8 Overview of patient reported outcome measures used in the thesis

Category	Name	Items (n)	Score	Cut-off/norm. data	Implication	Paper
Gastrointestinal symptoms	GSRS-IBS [177]	Total items (13)	13-91	None	High score-more symptoms	II, III, IV
		Pain (2)	2-14			
		Bloating (3)	3-21			
		Constipation (2)	2-14			
		Diarrhea (4)	4-28			
		Satiety (2)	2-14			
Coeliac disease symptoms	CSI [174]	Total items (16)	5-80	≤30 ≥45	Good QoL Poor QoL	III
Fatigue	GBB [178]	Total items (6)	0-24		High score - more fatigue	IV
		Weakness (1)	0-4			
		Sleepiness (1)	0-4			
		Exhaustion (1)	0-4			
		Tiredness (1)	0-4			
		Dizziness (1)	0-4			
		Fatigue (1)	0-4			
Anxiety and depression	HAD [179]	Total items (14)				IV
		Anxiety (7)	0-21	≥8	Anxiety	
		Depression (7)	0-21	≥8	Depression	
HRQoL	SF-36[180]	Total items (36)*	0-100		High score-high HRQoL	IV
		Physical functioning (10)	0-100	88.7		
		Role physical (4)	0-100	83.0		
		Role emotional (3)	0-100	84.1		
		Bodily pain (2)	0-100	74.4		
		Social functioning (2)	0-100	85.7		
		Mental health (5)	0-100	77.9		
		Vitality (4)	0-100	58.5		
		General health (5)	0-100	79.3		
Any symptoms	VAS	Pre-selected items within gastrointestinal and fatigue symptoms	0-100 mm		High score-more symptoms	II, III, IV

GSRS-IBS, Gastrointestinal Symptom Rating Scale IBS-version, CSI, Coeliac Symptom Index, GBB, Giessen Subjective Complaint List, HAD, Hospital Anxiety and Depression Scale, HRQoL, Health related quality of life, SF-36, Short Form 36 * item "Change in health" is not a real item and therefore not listed, VAS, visual analogue scale.

Comparison of symptom scoring methods

In paper II the result of the open bread challenge was retrospectively evaluated against suggested cut-offs for symptom change. A symptom increase of ≥30 % as response to gluten in a standardised challenge was considered as a relevant worsening of symptoms according to the Salerno experts criteria [139]. Furthermore, a symptom increase of ≥20 mm on VAS was considered a clinically relevant increase of symptoms when challenged to standardised gluten amount in a research setting [119]. These two cut-offs were applied to the results of the open bread challenges and compared by absolute and specific agreement.

3.7 Sample size and power calculation

The sample sizes of the study in paper I was not based on power calculation.

In paper II a retrospective power analysis was performed in Stata. Mean (SD) mm overall symptoms assessed by VAS during challenge was 67 (26) for NCGS (n=36) and 41 (15) for non-NCGS (n=6), and significantly different (p=0.001). With a significance level of 0.05, there was 88 % power to detect this difference in VAS score between 36 NCGS subjects and 6 non-NCGS subjects (Stata 14, College Station, TX: Stata Corp 2015 LP).

In paper III the sample size was based on the 20 subjects in the study by Leffler et al. [72]. A post-hoc sample size calculation using the primary end-point results (i.e. Marsh type 3 at end of challenge) in our study vs Leffler et al. (0.26 vs 0.70 with α=0.05 and β=0.20), revealed that a number of 17 subjects completing the study protocol would have been sufficient.

In paper IV the sample size was calculated prior to the study and was based on paired t-test of differences between two challenges within the same subject. The level of significance was set to 0.02 to account for pairwise comparisons between challenges (0.05/3). Earlier studies reported a GSRS-IBS mean difference of 1.5 units and a standard deviation of 3.2. With 80 % power and a two-sided significance level of 0.02 we needed 66 subjects to detect such a difference, given an anticipated drop-out of 30 % and six sequences of challenges (Stata 14, College Station, TX: Stata Corp 2015 LP).

3.8 Statistical analysis

Descriptive data were presented as frequencies (%), means (SDs) or medians (IQRs) in all papers. Statistical analysis was performed using SPSS 22.0 and 24.0 in papers I, II and IV. In paper III statistical analysis was performed using GraphPad Prism 7.02. Two-sided p-values <0.05 were considered significant.

In paper I continuous variables were analysed by two-sample t-test or Mann Whitney U-test, and categorical variables by chi-square test.

In paper II changes in symptoms from baseline to challenge for the whole group were tested by the Wilcoxon signed rank test. The two groups, NCGS and non-NCGS, were compared by the Mann Whitney U test. Comparison between the two groups as regards sex was performed by a chi-square test. Spearman correlation coefficient was calculated to estimate the associations between the symptom scores for overall symptoms, abdominal pain and bloating by VAS and total score for GSRS-IBS and the pain and bloating dimensions. Agreement between the scoring methods was estimated by absolute agreement (the proportion of patients on the diagonal, P_A) and Kappa (κ). Strength of agreement was evaluated according to the Kappa cut-offs given by Landis & Koch [181]: $=0.01 \leq \kappa \leq 0.20$ poor, $0.21 \leq \kappa \leq 0.40$ fair, $0.41 \leq \kappa \leq 0.60$ moderate, $0.61 \leq \kappa \leq 0.80$ substantial and $0.81 \leq \kappa \leq 0.99$ excellent agreement. McNemar test was used to test symmetry. Specific agreement was also calculated, expressing separately the agreement for the diagnosis of NCGS (positive agreement, P_{pos}) and non-NCGS (negative agreement, P_{neg}) using the formulas in de Vet et al [182].

In paper III normally distributed data were analysed by paired t-test or one-way analysis of variance with post-hoc Dunn's adjustment test for multiple comparisons relative to baseline. Wilcoxon signed rank test was used for non-normal paired data. Statistical analysis was done on GraphPad Prism V. 7.02 (GraphPad Software, La Jolla, California, USA) and SPSS (IBM SPSS Statistics V. 22.0, North Castle, New York, USA).

In paper IV differences between the challenge responses were analysed by linear mixed model and included multiple pairwise comparisons between challenges with Bonferroni corrections. Subjects were modelled as random with a random intercept at participant level. Challenge, period and sequence were modelled as fixed effects. Since we found no significant effect of sequence for any of the outcome variables, sequence was removed from the models. Baseline values were added as covariates. Day was included in the analysis of VAS symptom scores. We tested for interaction between challenge and period, and when significant, effect of challenge was analysed by linear mixed

model within each period. One-way analysis of variance was used for variables with skewed distribution where data was ln transformed before analysis.

3.9 Ethics

All four studies were performed in accordance with the Helsinki Declaration. The clinical trials in papers I, III and IV were approved by the Regional Committee for Medical Research Ethics (REK Sout/East) and registered at http://clinicaltrials.gov, with trial identifications NCT01100099 and NCT02464150, respectively).

The study of paper II was approved by the local Privacy Commissioner for Research at Oslo University Hospital, Division for patient security and quality with the project identification number 2014/16821. Signed informed consents were obtained from all subjects.

The manuscripts of papers I and III were prepared to the best of the investigators´ ability, paper II according to the standard criteria in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (http://www.strobe-statement.org) and paper IV according to the standard criteria in the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org).

4 RESULTS

Paper I

Twenty-three subjects with biopsy verified coeliac disease on a gluten-free diet and 34 HLA-DQ2+ NCGS subjects on a self-instituted gluten-free diet were investigated. The groups were comparable although women were slightly more frequent among the NCGS subjects than among coeliac disease subjects, 30 of 34, and 16 of 23, respectively (p=0.08).

Diet adherence in NCGS subjects was fair to good and did not differ significantly from adherence in subjects with coeliac disease (83 % vs 68 %, p=0.21). NCGS subjects were mainly self-educated in gluten-free diet compared to coeliac disease subjects (91 % and 39 %, respectively, p<0.001). The gluten level varied thirteen-fold (14 000-181 400 mg/kg) in samples from 10 different brands of regular white bread (n=11). In non-adherent subjects, there was no significant difference in gluten exposure between coeliac disease and NCGS (10 vs 138 mg/day, p=0.83). Finally, there was no significant difference in under-reporting between coeliac disease and NCGS subjects (BMR factor 1.23 vs 1.32, respectively, p=0.87), or between adherent and non-adherent subjects (BMR factor 1.26 vs 1.36, respectively, p=0.93).

Paper II

Fifty-six patients (44 women) self-instituted on gluten-free diet for a median (IQR) of 16 months (4, 37) with mean (SD) age 41 years (15.4) and median (IQR) BMI 22.6 kg/m^2 (20, 27) were studied. The examination of NCGS by an open bread challenge resulted in 47 patients (85 %) diagnosed as NCGS and nine non-NCGS. No significant differences were found between NCGS and non-NCGS as regards sex, BMI and duration of gluten-free diet ($0.50 \leq p \leq 0.95$), but the non-NCGS patients were significantly older than the NCGS patients (means 54 and 38 years, respectively, p=0.005).

Total GSRS-IBS score and overall symptoms by VAS increased significantly during wheat challenge in NCGS (p<0.001), but not in non-NCGS subjects (p=0.12 and p=0.08, respectively). Total GSRS-IBS challenge score and overall symptoms by VAS were significantly higher in NCGS than in non-NCGS subjects (53 vs 37, p=0.004 and 76 vs 39 mm, p=0.02, respectively).

Applying the Salerno and Monash cut-offs, 35 (63 %) and 42 (75 %) would be classified with NCGS, respectively. According to total GSRS–IBS absolute agreement was lowest between clinician's diagnosis and Salerno cut-off (63 %) and highest between Salerno and Monash cut-offs (88 %). Further, there was higher positive than negative agreement in all comparisons. Lowest specific

agreement was found between clinician's diagnosis and Salerno classification (P_{pos}=83 %, P_{neg}=53 %) and highest between Salerno and Monash classification (P_{pos}=91 %, P_{neg}=80 %).

Paper III

Twenty subjects (16 women), with mean (SD) age 42 years (16.5) and mean (SD) BMI 23.8 kg/m^2 169 (3.9) were included in the 14-day gluten challenge. The mean duration of gluten-free diet was 119 months, ranging from 6 to 473 months. Seventeen subjects were HLA- DQ2.5 and the remaining three were HLA-DQ8.

The average villous height to crypth depth ratio (Vh/Cd) changed significantly from 2.70 at baseline to 2.26 on day 14 of gluten challenge (p=0.002). Seven of 19 subjects had biopsy Vh/Cd < 2.0 on day 14, but two had biopsy Vh/Cd < 2 already at baseline. Hence, villous blunting at the end of challenge occurred in 5 of 19 subjects, and proved the efficacy of the gluten that was also used in the NCGS challenge study. Using cut-off for clinical significant absolute change in Vh/Cd ≤ 0.4 as proposed by others [183], we found significant decrease from baseline to day 14 in 10 of 19 subjects. The mean IEL count increased significantly from 23.5 at baseline to 40.9 on day 14 of gluten challenge (p<0.001). The frequency of HLA-DQ:gluten tetramer-binding T-cells increased by more than 100 % on day 6 in 12 of 15 subjects.

Symptoms, as scored by the CSI, increased significantly (p=0.002) from baseline to the end of challenge from a median (IQR) score of 24 (7) to 27 (8) on a 16–80 scale. VAS scores showed significant changes in stool consistency from baseline to week 1 (p=0.046), and in flatulence from baseline to week 2 (p=0.019).

Paper IV

The 59 subjects (53 women) that completed all three challenges had a mean (SD) age of 44 (4) years and mean (SD) BMI of 24.4 kg/m^2 (12), and had been on gluten-free diet the last median (IQR) 20 months (10, 48). According to the Rome III criteria, 18 subjects were defined as having IBS.

There was a significant difference in mean overall GSRS-IBS between gluten, fructan and placebo challenge, mean (SD) scores were 33.1 (13.3), 38.6 (12.3) and 34.3 (13.9), respectively (p=0.04). The score after fructan challenge was borderline significantly higher than after gluten challenge (p=0.05), and no differences were found for fructan versus placebo (p=0.19) and gluten versus placebo (p=0.99). No significant effect of gluten was found for any symptom, but 13 subjects had highest symptom score by overall GSRS-IBS after gluten challenge.

The fructan challenge induced consistently highest scores in all GSRS-IBS dimensions, but the difference was significant only for bloating where mean (SD) scores for gluten, fructan and placebo were 9.3 (3.5), 11.6 (3.5) and 10.1 (3.7), respectively (p=0.004). The fructan GSRS-IBS bloating response was significantly higher than after gluten challenge (p=0.003), but not higher than after placebo challenge (p=0.07). There was no significant difference in GSRS-IBS bloating between gluten and placebo challenge (p=0.84).

Daily overall gastrointestinal symptoms by VAS was highest after fructan challenge in period two, but the difference between the challenges was not significant in either of the periods.

There was a significant difference in SF-36 vitality scale scores between gluten, fructan and placebo challenge, mean (SD) 44.3 (25.2), 38.2 (23.4) and 44.4 (24.3), respectively (p=0.04). The GBB dimension weakness were significantly different between gluten, fructan and placebo challenge, 32.8 (30.0), 42.5 (26.6) and 33.5 (29.7), respectively (p=0.02). In the pairwise comparisons we found that the vitality score was significantly lower and weakness significantly higher after fructan challenge than after gluten challenge (p=0.04 and p=0.02, respectively). No significant differences were found in fructan versus placebo or gluten versus placebo for the two variables ($0.11 \leq p \leq 1.0$). Thirteen participants had the highest overall GSRS-IBS score after consuming gluten, 24 had the highest score after consuming fructan, and 22 had the highest score after consuming placebo. No significant differences were found for the other SF-36 scales and measures for fatigue, or for other extra intestinal symptoms ($0.10 \leq p \leq 0.96$).

5 DISCUSSION

First, we found that adherence to the gluten-free diet did not differ significantly between coeliac and NCGS subjects. Second, we found that an open wheat challenge with non-standardised symptom evaluation resulted in 85 % diagnosed with NCGS, higher than suggested standards. Third, diagnostic markers changed significantly in coeliac disease subjects after a 14-day gluten challenge. Finally, self-reported gluten sensitive subjects without coeliac disease recorded significantly higher overall gastrointestinal symptoms after fructan challenge compared to gluten. No significant effect of the gluten challenge was found.

5.1 Methodological considerations

5.1.1 Study samples

The subjects were recruited in the period 2009-2016 which covers the years were the public awareness and scientific research of NCGS increased substantially. There was a great willingness to contribute to research in this group, probably since many had experienced distrust and insufficient follow-up by the health care system. In the RCT of paper IV with the most comprehensive intervention, the drop-out rate was only 6 %. Practical and economic constraints restricted the recruitment to the southern east of Norway in all the studies. All the studies were carried out at the Oslo University Hospital, Rikshospitalet, one of very few sites that have offered a diagnostic workup for these patients.

Inclusion criteria for the self-reported gluten sensitive subjects in paper I were not as strict as the criteria in papers II and IV, in that they were not properly investigated for coeliac disease. Moreover, the subjects of paper II were exclusively referred patients, in contrast to subjects of papers I, III and IV which had a mix of referred patients and responders to public advertisements. Thus, both time span, selection and referral bias may have influenced the composition of the study samples. However, comparing the characteristics of the sample in papers I, II and IV in terms of gender, age and diet adherence, the samples appeared to be similar.

The subjects of the Paper IV study were recruited in accordance to strict inclusion criteria over a short period of time. Heterogeneity is a common characteristic of the NCGS population [141], but must also be considered as possible disturbance in interpretation of the results. We abstained from baseline interventions of the study sample in order to make the subjects present as close to a clinical setting as possible. However, in regards to gender, thyroid disease, IBS and coeliac disease in close family our sample was very much alike the samples described in other challenge and cross-sectional studies [119, 121, 122, 140, 184, 185]. Further, we did not find any effect of any of these factors on the challenge outcome.

Regarding adequate exclusion of coeliac disease and coeliac disease serology, our sample was more homogenous than in previous challenge studies [119, 184].

5.1.2 Study design

A cross-sectional design was applied for the studies of papers I-II in order to compare groups retrospectively. The design in the paper III-study was an uncontrolled intervention. Controlled studies have far greater validity than uncontrolled interventions. However, the two-week gluten challenge of coeliac disease subjects aimed to assess change from baseline and was designed to validate the use of two-week gluten challenge in the diagnostic setting [72].

Crossover design

The crossover design of paper IV was chosen to enable blinding of the dietary interventions. The design is rigorous and therefore has several advantages. First, the influence of confounding covariates was reduced because the subjects served as their own control. Second, the crossover design was statistically efficient and allowed fewer subjects than a parallel study [186, 187]. The crossover design is particularly suitable for IBS or NCGS, chronic and stable diseases where the treatment intend to alleviate the disease condition, not cure it. A common disadvantage with the crossover design is the carryover effect that can bias the interpretation of the result [188]. Carryover effects are difficult to measure and should not be ignored. Washout periods in between each challenge intend to diminish the impact of the carryover effect. Our washout periods seemed to be of sufficient length, since symptom scores did not differ from baseline, indicating that there were minimal symptoms to carry over to the next challenge.

A crossover design should be uniform across sequence (ABC-CBA) and periods (challenge week 1-3). Then, there would be no effect of sequence or period biasing the effect of challenge. However, we observed an effect of period on the gastrointestinal symptom scores by VAS. It indicated that the effect of challenge was not the same across the periods. The placebo scores were highest in period 1 and the fructan scores were highest in period 2. Although the washout appeared to be long enough, we speculate whether a prolonged washout of at least two weeks could diminish the effect of period. Further, one week of single blinded placebo challenge prior to the challenge could possibly alleviate the expectations prior to the first period. However, the period effect is almost impossible to overcome completely because of increased subject comfort and knowledge in later periods, and improvement in skill and technique of the study team members.

Background diet

The subjects´ background diet may influence the endpoints; however, to control the background diet during a dietary intervention is a tricky exercise [186]. One study has succeeded in doing this. Biesiekierski et al. succeeded in providing all food to the subjects in the crossover challenge in IBS patients [119]. It requires enormous effort from the investigators and reduces the self-determination of the subjects. However, the effort reduces background noise and yields high quality results. A limitation with our challenge study was that we did not control the background diet. We had two reasons for not doing it. First, we aimed to design the study as close to the clinical setting and real life as possible. Second, we wanted to spare participant burden and investigation resources. To overcome that we did not provide the background diet, we instructed the subjects to record their diet for 7 days before they entered the interventions to assess diet adherence, and told them not to change their habitual diet during the challenge periods. However, compliance was not checked during the study, and changes in the background diet could therefore not be excluded.

5.1.3 Dietary assessment

The 3-day weighed food record (paper I) and the 7-day food diary record (paper IV) were both prospective and open ended surveys which allowed abundant information to be collected independently of the subjects' memory. However, both methods require a high level of motivation and a relatively large burden is passed onto the respondents [189]. Moreover, some subjects may improve their dietary habits unintentionally through self-reflection. Some subjects may also change their diet intentionally to avoid burden on response, choose not to report actual intake or even drop out [189]. These limitations may result in under reporting of dietary intake. Knowing that gluten-free diet was an inclusion criterion for participation may have resulted in underreporting of gluten-containing food. However, the motivation a genuine interest in participating in research and own follow-up is believed to result in an honest contribution. Factors such as seasonal variations, illness fluctuations and travelling may always influence dietary assessment. The open ended dietary assessment methods entail a considerable effort from the investigators in terms of data collection, entry an analysis. However, an important reason why we chose the open ended methods was that assessment of gluten-free diet requires manually calculation of gluten-free foods that are not included in the Norwegian Food Composition Table. The validated, pre-coded food frequency questionnaires developed for the Norwegian adult population were unsuited for a population on gluten-free diet.

The purpose of calculating gluten exposure in paper I required a detailed description of the diet. This was achieved by choosing the weighed food record. A weakness, however, is the short time period which limits the generalization of the results. The purpose of the dietary assessment in the RCT in

addition to evaluate diet adherence, was to describe the gluten-free diet in NCGS in general for future publications. That required a longer period of time, and therefore a 7-day food record was suitable.

5.1.4 Gluten-free diet adherence

Gluten-free diet is the only available treatment for coeliac disease, and follow-up of coeliac patients includes evaluation of diet adherence, especially in cases with persisting symptoms or delayed mucosal healing. Despite the clear need of a standardised instrument, validation of a test to measure gluten-free diet adherence has been difficult. Studies of conventional serologic tests have not yielded favourable results [190-192]. Several approaches of variable reliability are available; patient self-assessment, dietary assessment, serological and histological testing. However, the current gold standard is still considered to be evaluation by an expert dietitian with extensive experience in dietary education and follow-up of new and treated coeliac patients [193]. Where there are no objective biomarkers to monitor, such as in NCGS, adherence can only be evaluated by dietary assessment or by a dietitian. Further, the importance of dietary strictness may be different between NCGS and coeliac disease.

With the exception of the study of paper II, gluten-free diet adherence was determined by a multilevel assessment to ensure a result as reliable as possible. In paper I where the purpose was to compare adherence between groups we used patients' self-assessment and dietary assessment by weighed food record. These methods were supportive to the dietitian administered questionnaire considering diet understanding, diet practice and risk behaviour. The assessment of gluten-free diet of the study in paper II was exclusively based on the dietitian's dietary interview and the patients' self-assessment, since the purpose was to ensure that the patients were on a gluten-free diet. We used the multilevel approach in the RCT of paper IV to ensure that the study subjects were strictly adherent. Here, the dietitian questionnaire was improved by including information from focus groups of coeliac adults and by using background information from Leffler´s CDAT [170, 193-196]. This questionnaire was self-administered and recorded in presence of the dietitian at the first study visit. Good adherence was required for participation, but single accidental transgressions the last six months such as having had a meal on a vacation or been served a meal at friends with unintended content of gluten were accepted.

Both Biagi et al. and Leffler et el. have developed standardised questionnaires for assessment of adherence [170, 197]. We chose not to use these tools since they were aimed to measure the gluten-free diet adherence in coeliac disease and the level of adherence in the gluten-free diet in NCGS may not need to be as strict as in coeliac disease. Further, there was no reference method to use, since diet adherence in NCGS had not been described before. Although the dietitian assessment is regarded as gold standard, a limitation is the lack of standardisation that hampers comparison with future studies.

5.1.5 Gluten challenges

Open challenge

When the National Administration of Labour and Welfare decided that reimbursement for gluten-free diet was applicable for individuals with gluten sensitivity without coeliac disease, a standardised challenge and confirmation by a gastroenterologist was required. To meet this requirement an open bread challenge with a standardised symptom recording was developed at Oslo University Hospital, Rikshospitalet in 2009. The fundamental attitude from the clinicians was that the patients were always right. Patients were not contradicted in their experience of having adverse reactions to wheat, bread or cereals or when they perceived gluten sensitivity. There were good reasons for choosing an open challenge to manage these patients: the wheat challenge mimicked the real life setting, it was a method close to how other food intolerances are managed and easy for both patient and clinician to administer. The method was accepted by the Norwegian Labour and Welfare Service and worked for the purpose of getting reimbursement for expenses related to gluten-free diet, and of the patient having a diagnosis. However, the method has limitations for the purpose of defining NCGS in the individual. The open challenge is known to overestimate positive outcomes caused by the nocebo effect [5, 186, 198]. Further, wheat fructans known to reduce symptoms in individuals with IBS if removed from the diet, had not been considered in this workup [156, 199]. The coexistence of gluten and fructans in wheat does not allow distinguishing between reactions caused by gluten or fructans. The open wheat challenge procedure of Oslo University Hospital, Rikshospitalet was therefore terminated in 2015.

Blinded challenge

For conditions that manifest mainly with subjective symptoms, such as NCGS and other food intolerances, there have been strong indications and recommendations for the use of DBPCFC [186], especially when it is not possible to contrast the results with objective biomarkers [198]. The muesli bars developed by Monash University, Australia allowed blinded intervention. Some subjects did observe minor differences in consistency and taste between the three types of muesli bars, but they were not able to differentiate gluten, fructan and placebo. Thus, the similarity was not perfect but the blinding was successful.

Although DBPCFC is considered the gold standard to define adverse reactions to food, a reappraisal of the procedure has revealed that the method has many pitfalls and is not as ideal as has been believed for a long time [15, 200, 201]. The limitations include poor standardisation, high costs, requirement of well-equipped facilities and trained personnel in addition to sensitivity and specificity issues [198]. In clinical trials, however, where successful blinding is possible and the aim is to prove or disprove the existence of a condition or to define the culprit of symptoms, the DBPCFC remains the preferred method [36].

However, an obstacle with the method used in NCGS patients is the large nocebo[1] effect, the response to placebo [119, 184, 185, 202]. In a clinical context, this phenomenon may cause false positive results. The problem arises of how to separate a nocebo response from a specific response with confidence, and to define who will benefit from a gluten-free diet. Therefore, DBPCFC is all but a gold standard for the clinical setting. The method is suggested to be supportive to diet history in investigation of adverse reactions to food [203]. For the long term follow-up of the individual patient with presumed NCGS in a clinical setting, standardised elimination and open challenge should be sufficient [198].

The Australian muesli bars had previously not been used in any challenge. They were developed to enable successful blinding and mimic gluten-containing food. The moderate doses of gluten and low doses of fructans were chosen to resemble the clinical situation as closely as possible. The gluten was evidently biologically active as subjects with previously biopsy-proven coeliac disease who were challenged with the gluten muesli bars for 14-days developed significant changes (paper III). Further, the dose of 5.7 g gluten was believed to be adequate since previous studies have been able to demonstrate symptom responses on equivalent and lower amounts of gluten [184, 202].

5.1.6 Patient reported outcome measures

Patient reported outcome measures are useful for the aim of comparing means, comparing changes and "responder" proportions, especially for conditions where the clinical manifestations are highly subjective, such as in IBS and NCGS. Disease specific measures are developed for coeliac disease and IBS [174, 177, 204-208]. An outcome measure needs to be translated and validated to be a reliable measure in countries and conditions other than the original setting. Clinical experience and previous studies within our research group governed the choice of outcome measure in the present studies [132, 173, 209, 210]. We considered our tools from clinical practice and research as more suitable and valid than other outcome measures adapted for IBS (ref), although an obvious limitation with GSRS-IBS and GBB in the present studies is the lack of validation for a Norwegian setting and for the NCGS population. However, the GSRS-IBS has been widely used in clinical investigation of coeliac disease, IBS and NCGS and was also used in Brottveit's research of coeliac disease and NCGS [173]. Another limitation with the GSRS-IBS is the lack of cut-off values [177]. However, as outcome measures in general, GSRS-IBS works well for the assessment of effect of intervention and for the purpose of comparing different interventions [211]. Recall bias may occur when recording symptoms 7-14 days retrospectively by GSRS-IBS as in the study of papers III and IV. However, the daily scored VAS scales that have been used in similar challenge studies [119, 202] were consistent with the main findings of GSRS-IBS.

[1] A psychological phenomenon, in which the recipient perceives a deterioration in condition as response to a sham or dummy intervention, in this case the challenge.

5.2 Interpretation of results

5.2.1 Diet adherence in coeliac and non-coeliac patients

Despite different case histories and motivation for dietary changes in coeliac disease and NCGS patients, we found minimal differences in the gluten-free diet between the groups. Adherence in coeliac disease patients seemed slightly, but not significantly better than in NCGS patients, so the prudent expectation that patients with coeliac disease had a stricter gluten-free diet than patients with NCGS was discarded. However, with increased sample size a small difference might have been detected. A type two error cannot be excluded.

The level of adherence to the gluten-free diet needed in NCGS has been unexplored until now. However, there is no evidence that the gluten-free diet in NCGS need to be as strict as for coeliac disease patients. In NCGS there is currently no defined mechanism of gluten as symptom trigger or known long-term consequences of gluten exposure. Thus, a level of adherence that allows acceptable symptom relief in the individual may be sufficient.

The 83 % of coeliac disease patients with good adherence corresponded with existing knowledge [212, 213]. However, a systematic review found that rates for adherence ranged from 42 % to 91 % depending on definition and method of assessment [214]. More recently, a study using the CDAT found that 75 % of coeliac disease adults had adequate adherence to gluten-free diet (CDAT≤13) [212]. In 2260 Dutch coeliac patients, 96 % reported very stringent (50 %) or sufficient diet as response to one single self-reported question about diet adherence [213]. An Indian study found that 53 % of coeliac patients had excellent or good adherence based on how patients categorised gluten-free and gluten-containing foods from a list [215]. The level of adherence increased to 92 % with repeated counselling, which highlights the importance of professional diet education. If the 39 % of coeliac patients that were self-taught in paper I had been professionally educated, the proportion of patients with good adherence may have increased.

Transgression did occur in both coeliac disease and NCGS patients, mostly by intake of regular beer, bread or pizza. Considered the finding of two times the expected level of gluten in regular bread, serious consequences in coeliac disease by repeated intended intake of regular bread cannot be excluded. The findings indicated that the grade of adherence is not automatically stricter in coeliac than in NCGS individuals.

5.2.2 Clinical workup of NCGS

Open wheat challenge in clinical practice

The open wheat challenge is an example of how the health care system (Oslo University Hospital, Rikshospitalet) dealt with a new type of patients to the best of its ability. In the sum up of the clinical material of 2009-2015 we found a high internal consistency in that the highest symptom scores during challenge was found in the patients that were diagnosed with NCGS and lowest in non-NCGS. Overall, this finding confirmed that the investigation succeeded in classifying correctly as regarded the symptoms. The 85 % prevalence of NCGS diagnosis was not surprising because of the highly selected patient material.

However, the result must be interpreted cautiously because of the methodological limitations of the open challenge [3]. Further, the possible reimbursement may have motivated patients to seek the diagnosis.

Symptom scoring

Management of less defined conditions such as IBS and NCGS could be more straight forward in clinical practice with standardised cut-offs for symptom change. However, symptom relief and symptom increase are highly subjective definitions, and such standardisation would probably help the clinician more than the patient. It is difficult to standardise level of symptoms in conditions with subjective manifestations. In a clinical setting the most meaningful approach is to define the presence or absence of symptoms at baseline and then measure changes as response to intervention. Whether or not the change is significant or satisfactory will depend up on the individual. Thus, evaluation of symptom changes in clinical practice is possible and meaningful without cut-offs.

In the scientific context defined cut-offs facilitate the ability to describe and compare groups. In Biesiekierski et al the 20 mm minimum change of symptoms was set to separate between positive and negative response to gluten challenge [119]. In assessing pain in children 20 mm has been defined as "little more" and 40 mm as "much more" of the symptom [216], and 22 mm has been considered as minimal clinical change for measuring nausea in adults [175]. The suggested minimal 30 % symptom change as response to the shift from normal diet to gluten-free diet, and as response to a gluten challenge was an attempt to standardise the diagnostics of NCGS [139]. However, the high prevalence of placebo responses in such challenges reduces the clinical value of this standard.

5.2.3 Exclusion of coeliac disease

One inclusion criterion for subjects with self-reported gluten sensitivity in the crossover gluten challenge (paper IV) was adequately exclusion of coeliac disease. Many reported that they had undergone a gastroscopy with duodenal biopsy while on gluten-containing diet. However, further elaboration revealed cases were the gluten exposure was too short and/or too low (< 4 slices of bread in < 2 weeks). These subjects were considered non-eligible for participation. There was a risk of false negative result for coeliac disease that could lead to an incorrect diagnosis of NCGS. Previous studies investigating NCGS may have suffered from inadequate exclusion of coeliac disease of the study subjects and therefore been biased by coeliac disease subjects [108, 217]. A less invasive method could simplify the exclusion or confirmation of coeliac disease for those already on a gluten-free diet. However, the 14-day gluten challenge was not enough to detect coeliac disease by conventional histological evaluation of duodenal biopsies. This study supported clinical decision making in favour of longer duration of gluten challenge.

The optimal dose of gluten in a short challenge is not known and should probably be seen in conjunction with the duration of the challenge. One study of 6-week gluten challenge in adults in mucosal remission used daily doses of 1.5, 2, 3 and 6 g gluten, showing a clear dose response effect, diminishing towards the higher doses, as doses of 3 and 6 g were both able to give Vh/Cd ≤2 in about 70 % of the subjects [218]. It is, however, not clear when the villous blunting occurred during the 6-week time frame. Thus, although a daily gluten dose of 3 g may be sufficient for a 6-week challenge, it may not be sufficient for a 14-day challenge, as seen in our study where the use of 5.7 g gluten daily only gave Vh/Cd ≤2 in approximately one-third of the subjects. An alternative strategy for response evaluation could be repeated sets of duodenal biopsies, before and after gluten challenge. This approach could provide a more sensitive readout than the recommended practice of only taking one set of biopsies at the end of a gluten challenge. Applying the absolute change in Vh/Cd of 0.4 and an IEL change of about 50 % in H&E-stained biopsies, the sensitivity of the 14-day gluten challenge increased to 50 % but was still found unsatisfactory [183]. A twofold change in gluten-specific T-cell response in blood, measured by HLA-DQ:gluten tetramers, was detected after 6 days of gluten challenge in a majority of subjects with coeliac disease in remission. This approach could be applied to detect coeliac disease after a short gluten challenge. The method is promising but needs further evaluation.

5.2.4 Symptom inducers in NCGS

Previous and recent publications and editorials have questioned the role of gluten as symptom trigger in people without coeliac disease and discussed the ambiguous overlap between IBS and NCGS, but with a restricted number of good clinical trials [39, 118, 133, 155, 219-221]. It is beyond controversy that intake

of wheat, rye and barley can induce symptoms in individuals without coeliac disease [222]. Further, there are sources of evidence that some individuals may benefit from a gluten-free diet without having coeliac disease. However, not all effects of a gluten-free diet are due to the removal of gluten. Randomised double-blind placebo-controlled gluten challenges have shown that gluten induce more symptoms than placebo in subjects that self-report gluten sensitivity [107, 109]. However, double-blind crossover re-challenge studies have failed to identify specificity of gluten in inducing symptoms in all but possibly a minority (<10%) of patients with self-reported NCGS [217]. Further, there are no defined predictors of response to a gluten-free diet. Large placebo responses in challenge studies demonstrate how difficult it is to define who will benefit from a gluten-free diet [119, 184, 185, 202]. Further, alteration of the gluten content of the diet has effects on dietary constituents in addition to gluten such as the fructans. Consequently, research has gradually looked beyond gluten to search for the real culprit and meanwhile suggested that non-coeliac wheat sensitivity is a more correct name [141, 220, 223].

The present crossover challenge is the first randomised clinical trial to study the effect of fructans (without gluten) in individuals with self-reported NCGS. The most certain finding was the lack of difference between gluten and placebo responses. This finding alone weakens the role of gluten in NCGS. The gluten dose was certainly moderate (5.7 g). Nevertheless, lower doses have shown to induce symptoms in other challenge studies of suspected NCGS individuals [184, 202]. Several blinded, crossover studies have claimed in their conclusions that the presence of NCGS is unequivocally present in a proportion of patients believing they are gluten sensitive, and strong recommendations that gluten-free diet should be used in patients with IBS have been made on the basis of such data. In these studies, patients with greater gluten response have been labelled as having NCGS. For instance, in the study by Zanini et al., patients were asked to identify which of the rechallenged substance was gluten, based upon their symptoms [185]. One-third identified gluten and the authors then defined that subgroup as having NCGS. The same interpretation was applied in the study of Elli et al. [202]. Di Sabatino also found that gluten induced significantly more symptoms than placebo. However, only three subjects could be defined as having a gluten specific response when a statistical approach such as two standard deviations was applied [184].

The fructans induced significantly higher symptom score for overall GSRS-IBS and several sub-dimensions. The response to fructans strengthen the hypothesis that wheat fructans are the real symptom inducer rather than gluten. This picture fits well with the mechanistic effect of FODMAP on gastrointestinal symptoms which is already well studied and understood [136, 162, 199, 224]. The fact that the responses were not huge in magnitude is not unexpected as, in the context of usual food, cereal-based fructans will be ingested in association with other indigestible oligosaccharides as well as other FODMAP.

Originally, the fructan content of the muesli bar was not decided with the purpose of triggering symptoms, but to mimic the content of fructans in four slices of white wheat bread (2.1 g). Consequently, the fructan challenge almost doubled their habitual daily fructan exposure of 2.2 g/day. The amount is sufficient to cause symptoms [98]. However, the amount was still lower than the 5 g that did not induce gastrointestinal symptoms in healthy adults in the study of Erickson et al 2017 [225].

In addition to increase in the overall GSRS-IBS, the effect on GSRS bloating fitted well with the significant improvement of bloating as a response to low FODMAP diet reduction in IBS patients [156]. Likewise, the lack of fructan effect on bowel habits supported the lack of effect on appearances and fecal water content in a feeding intervention [226].

The effect of the fructan challenge was not restricted to abdominal symptoms. The SF-36 vitality scale was significantly lower and VAS weakness significantly increased as response to the fructan challenge compared to gluten and placebo. Improvement in quality of life in IBS patients has been found as an effect of low FODMAP diet [106]. Whether improvement in vitality and weakness are directly related to fructan exposure or secondary to the higher degree of gastrointestinal symptoms cannot be ascertained.

Wheat-generated symptoms may depend on combined exposure to gluten and fructans with synergistic actions. This combination was not studied here. It is also possible that fructans present naturally in the food matrix behaves differently to supplements of pure fructo-oligosaccharides added to the diet. Further, the fructo-oligosaccharide added in the muesli bars originated from chicory roots and might have different effect from the fructo-oligosaccharide in wheat. Other components of wheat, such as the ATIs and the lectin, wheat germ agglutinin, were not considered in the current study apart from not being able to detect the ATIs [45]. In vitro studies have found effect on cell activation of these components [45, 227], but in IBS and NCGS patients the pathogenic role of ATIs and wheat germ agglutinin is unexplored.

The results of the current study weakens the role of gluten as a symptom inducer in patients with self-reported NCGS, supported the report by Biesiekierski et al. in a blinded re-challenge study where the subjects were receiving a low FODMAP diet with tight control of background confounders [119]. In the initial run-in to the blinded re-challenges, Biesiekierski et al. taught the subjects how to minimize FODMAP in their diets, and this caused a uniform reduction of symptoms. This may have been a placebo effect, but the findings of the present study support that it was a specific effect of the reduction of total FODMAP. Biesiekierski et al. was not able to find any specific or dose dependent (3 and 16 g) effect of gluten in their randomised double-blind placebo-controlled challenge study.

5.2.5 Implications

Norway has been one of few countries that have provided governmental reimbursement for patients with NCGS, equivalent to what patients with coeliac disease receive. In the light of the present findings, this reimbursement may need reconsidering or implementation of more rigorous requirements. Clinicians may need to have focus on lowering dietary FODMAP before removing gluten from the patient´s diet. Overall, self-reported gluten-sensitivity without coeliac disease should be managed as IBS rather than an independent entity.

5.3 Limitations

An important limitation of the comparisons between coeliac disease and NCGS in paper I was the small number of subjects in each group, which influenced the number of diet recordings, the variety and number of analysed foods and the number of gluten-consuming subjects. For this reason type two errors cannot be excluded.

The number of NCGS subjects may have been overestimated in papers I-II due to the open bread challenge, which is known to create false positive results. Further, the challenge vehicle included several possible symptom-inducing components, and the symptom change was not evaluated in accordance to a standard.

A methodological weakness of the study in papers II-IV was the lack of validation of several of the patient reported outcomes measures. Despite long experience with the methods in clinic and research, the results must be interpreted with some modesty.

A possible limitation in generalizing from the findings of the 14-day challenge in coeliac disease patients of paper III was the low number of subjects. Further, coeliac disease patients who had a history of strong gluten-related symptoms were excluded to ensure that the subjects were able to complete the 14-day challenge and that evaluation of morphological response was possible.

Limitations of the randomised double-blind placebo-controlled challenge in Paper IV included no control of the background diet and no dietary assessment during the challenge to ensure that the subjects adhered strictly to the habitual gluten-free diet. Changes in the background diet with possible implications for the symptoms were not controlled. Muesli bars as challenge vehicle has to our knowledge not been used in gluten challenges before. Gluten was proved biologically active, however, the source of fructooligosaccharide was not tested. Further, the effect of time that appeared as a significant period by challenge interaction for the symptoms measured by VAS, was probably an effect of the subjects' expectation of distress, which is difficult to overcome in crossover studies. It

entailed different challenge effect between periods, which is not ideal in a crossover design. Repeated active and placebo challenges may overcome such period effect. Although there was no difference between baseline and washout symptoms, the period effect could have been reduced with increased length of the washout periods. Finally, the study did not include the combination of gluten and fructans together as a separate challenge arm. The possibility of a synergistic effect of the combined components cannot be ignored.

5.4 Future perspectives

Exploring the nature of gluten-free diet whether it is subjects with or without coeliac disease is of importance since it excludes bread and cereals as the most important staple food of the Western diet. Future studies should explore the nutrient composition of gluten-free diet applied by non-coeliac subjects.

Our findings propose that cereals are the most frequent source of gluten in transgressions of gluten-free diet. The results also indicate lack of standardised recipes regarding vital gluten as bread ingredient even within the same brand. Consequently, gluten challenge by a certain number of slices of white bread may give highly variable gluten loads. Whether the aim is to estimate gluten exposure as a cause of diet transgression or to standardise a gluten challenge in coeliac disease wok-up, it requires extended knowledge about gluten content of wheat flour and the amount of purified vital gluten added in bread and cereals during production.

The current guidelines for coeliac disease workup for subjects already on a gluten-free diet may be an obstacle of obtaining a correct diagnosis. A less invasive workup that is based on a short-duration gluten challenge, followed by blood test based on HLA-DQ:gluten tetramers as biomarker is promising but should be explored further.

Finding the alternative food component that is responsible for symptom induction in self-reported NCGS is important as it provides guidance on likely more efficacious and less restrictive dietary approach to giving symptomatic relief to the patients. The clinical challenge is how to define those few patients with specific gluten response. One clinical approach is to reintroduce a gluten-containing, low FODMAP food, such as sourdough spelt bread, after an elimination phase of the low FODMAP diet. However, even with clinical relevant symptom response to such a reintroduction, open or blinded, the gluten specificity of the symptoms would not be certain. Further aspects are suggested for future research:

- The fructan effect and lack of gluten response as well as the efficacy of muesli bars as challenge vehicle need to be replicated to prove the validity of the current findings.

- The effect of a low FODMAP diet should be further explored in the group of self-reported NCGS on self-instituted gluten-free diet.
- Mechanistic research in subjects with self-reported NCGS needs to focus beyond gluten.
- Studies designed to measure extra-intestinal symptoms as primary outcome are needed to explore effects beyond the gastrointestinal symptoms.
- The possibility of a synergistic effect of gluten and fructan in combination should be explored.
- The effect of gluten removal and reduction of fructans in the diet should be compared in an "all food provided"-setting.

6 CONCLUSIONS

Gluten-free diet adherence did not differ between coeliac disease and NCGS subjects. Diet adherence was fair to good in NCGS even though most of them were self-educated in gluten-free diet. Gluten content of bread differed greatly and certain brands contained more than two times the expected gluten level.

Open wheat challenges in clinical follow-up of patients with presumed NCGS from 2009 to 2015 resulted in 85% diagnosed as NCGS. Subjects diagnosed with NCGS reported significantly more gastrointestinal symptoms than non-NCGS subjects. An overestimation in the clinician′s diagnosis was probable since the prevalence was lower according to both the Salerno and Monash cut-offs classifications. Best agreement was found between the Salerno and Monash cut-offs, and lowest between clinician′s diagnosis and Salerno cut-off.

A 14-day gluten challenge was inadequate when villous blunting or increased coeliac disease specific antibody levels were used as outcome measures. Repeated biopsies taken before and after a short gluten challenge can increase the sensitivity of the test, but not enough to recommend this procedure. Longer duration challenge is required. Increase in CD4+ effector-memory gut-homing HLA-DQ:gluten tetramer-binding T cells in blood six days after gluten challenge was a more sensitive and less invasive biomarker that should be explored further.

The randomised, double-blind placebo-controlled crossover challenge study in subjects with self-reported NCGS showed that fructans emerge as a culprit without any evidence to implicate gluten. In other words, ‘self-reported NCGS’ is in the vast majority not ‘NCGS’, but rather likely to be a dose-related effect of fructans. The finding weakens the use of the term “NCGS” and raises doubts about the need for a gluten-free diet in such patients.

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APPENDICES

I. Ethical approvals
II. Participant consent forms
III. Notification of imported foodstuff
IV. Questionnaires

UNIVERSITETET I OSLO

DET MEDISINSKE FAKULTET

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Dato: 12.09.06
Deres ref.:
Vår ref.: S-06114

S-06114 **Cøliakidiagnose i en blodprøve**

Vi viser til brev datert 15.6.2006 vedlagt revidert informasjonsskriv med samtykkeerklæring.

Komiteen tar svar på merknader til etterretning.

Komiteen har ingen merknader til skjema for opprettelse av forskningsbiobank.

Komiteen har ingen merknader til revidert pasientinformasjon og samtykkeerklæring.

Komiteen tilrår at prosjektet gjennomføres og at forskningsbiobank opprettes.

Komiteen videresender skjema for opprettelse av forskningsbiobank og informasjonsskrivet samt komiteens vedtak til Sosial- og helsedirektoratet for endelig behandling av opprettelse av forskningsbiobanken.

Vi ønsker lykke til med prosjektet.

Med vennlig hilsen

Kristian Hagestad
Fylkeslege cand.med., spes. i samf.med
Fungerende leder

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Sekretær

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PERSONVERNOMBUDETS TILRÅDING

Til:	Gry Irene Skodje
Kopi:	Knut Lundin
Fra:	Personvernombudet ved Oslo universitetssykehus
Saksbehandler:	Henrik Lindgren Jensen
Dato:	22.04.2015
Offentlighet:	Ikke unntatt offentlighet
Sak:	Personvernombudets tilråding til innsamling og databehandling av personopplysninger
Saksnummer/ ePhortenummer:	2014/16821

Personvernombudets tilråding til innsamling og behandling av personopplysninger for prosjektet "Glutenprovokasjon ved mistent ikke-cøliakisk glutensensitivitet"

Viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er personvernombudets tilråding av prosjektet.

Med hjemmel i personopplysningsforskriften § 7-12, jf. helseregisterloven § 36, har Datatilsynet ved oppnevning av personvernombud ved Oslo Universitetssykehus (OUS), fritatt sykehuset fra meldeplikten til Datatilsynet. Behandling og utlevering av person-/helseopplysninger meldes derfor til sykehusets personvernombud.

Databehandlingen tilfredsstiller forutsetningene for melding gitt i personopplysningsforskriften § 7-27 og er derfor unntatt konsesjon.

Personvernombudet tilrår at prosjektet gjennomføres under forutsetning av følgende:

1. Databehandlingsansvarlig er Oslo universitetssykehus HF ved adm. dir.
2. Avdelingsleder eller klinikkleder ved OUS har godkjent studien.
3. Behandling av personopplysningene / helseopplysninger i prosjektet skjer i samsvar med og innenfor det formål som er oppgitt i meldingen.
4. Data lagres som oppgitt i meldingen. Annen lagringsform forutsetter gjennomføring av en risikovurdering som må godkjennes av Personvernombudet.
5. Vedlagte samtykke benyttes, inklusive markerte tillegg og endringer foretatt av personvernombudet. Eventuelle fremtidige endringer som berører formålet, utvalget inkluderte eller databehandlingen må forevises personvernombudet før de tas i bruk.
6. Kryssliste som kobler avidentifiserte data med personopplysninger lagres som angitt i meldingen og oppbevares separat på prosjektleders avlåste kontor.
7. Dersom formålet eller databehandlingen endres må personvernombudet informeres om dette.

8. Kontaktperson for prosjektet skal hvert tredje år sende personvernombudet ny melding som bekrefter at databehandlingen skjer i overensstemmelse med opprinnelig formål og helseregisterlovens regler.
9. Data slettes eller anonymiseres ved prosjektslutt01.01.2028 ved at krysslisten slettes og eventuelle andre identifikasjonsmuligheter i databasen fjernes. Når formålet med registeret er oppfylt sendes melding om bekreftet sletting til personvernombudet.

Prosjektet er registrert i sykehusets offentlig tilgjengelig database over forsknings- og kvalitetsstudier.

Lykke til med prosjektet!

Med vennlig hilsen
Henrik Lindgren Jensen
Personvernrådgiver
Oslo universitetssykehus HF
Stab pasientsikkerhet og kvalitet
Seksjon for personvern og informasjonssikkerhet

Epost: personvern@oslo-universitetssykehus.no
Web: www.oslo-universitetssykehus.no/personvern

Akershus universitetssykehus

Akershus universitetssykehus HF

Postadresse:
Postboks 95
1478 Lørenskog

Sentralbord:
02900

Org.nr:
NO 983 971 636 MVA

www.ahus.no

REK-PROSJEKT
PERSONVERNOMBUDETS UTTALELSE TIL UTLEVERING AV PASIENTJOURNAL

Til:	Knut Lundin, prof overlege, avd for transplantasjonsmedisin, OUS HF og Gry Skodje, klinisk ernæringsfysiolog
Kopi:	Kst Geir Arne Larsen, Gastrokirurgisk avdeling Jane Beate Bjur, seksjonsjef,Journalarkivet
Fra:	Personvernombudet ved Akershus universitetssykehus
Saksbehandler:	Marianne B Blair
Dato:	04.07.2015
Offentlighet:	Ikke unntatt offentlighet
Sak:	Personvernombudets uttalelse til innsamling og behandling av personopplysninger
Saksnummer/ Personvernnummer:	15-127

Personvernombudets uttalelse til innsamling og behandling av personopplysninger for forskning i prosjektet "Gluten- og fodmap-provokasjon ved glutensensitivitet uten cøliaki"

Prosjektbeskrivelse:
Bakgrunn:
Betegnelsen glutensensitivitet omfatter cøliaki, hveteallergi og ikke-cøliakisk glutensensitivitet. Felles for tilstandene er behandling med gluten- og hvetefri kost. Cøliaki og hveteallergi er veldefinerte diagnoser med standardisert utredning. Ikke-cøliakisk glutensensitivitet (NCGS) mangler presis definisjon, utredningen er ikke standardisert og sykdomsmekanismen er ukjent. Tilstanden er klinisk lik cøliaki, men uten intestinal inflammasjon eller positiv serologi. Det foregår internasjonal forskning for å øke kunnskapen NAV innrømmer grunnstønad ved positiv test på glutenprovokasjon hos spesialist, men definerer ikke hvordan provokasjonen skal utføres. Oslo Universitetssykehus, Rikshospitalet har i flere år utredet disse pasientene ved hjelp av standardisert, åpen glutenprovokasjon, der positiv test bekrefter NCGS. Metoden har svakheter som vi ønsker å forbedre ved å prøve ut en dobbeltblindet placebokontrollert provokasjon med gluten og fodmap hver for seg.
Målsetning:
Å forbedre utredningen av glutensensitivitet uten cøliaki ved å utvikle en standardisert og objektiv diagnostikk til bruk i klinikken: dobbeltblindet placebokontrollert glutenprovokasjon

Viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er et formelt svar på meldingen og gjelder kun utlevering av pasientopplysninger i prosjekt der Akershus universitetssykehus HF ikke har noen annen rolle. Forutsetningene nedenfor må være oppfylt før rekruttering av pasienter til studien kan starte.

Med hjemmel i Personopplysningsforskriftens § 7-12 jf. Personopplysningsloven § 31, har Datatilsynet, ved oppnevning av personvernombud, fritatt sykehuset fra meldeplikten til Datatilsynet. Forskningsprosjekter (studier) som omfatter høsting, lagring og tilgjengeliggjøring samt behandling av person-/helseopplysninger, meldes derfor til sykehusets personvernombud, se særlig helseregisterloven § 3 om formål og § 6 om alminnelige vilkår for å behandle helseopplysninger.

Personvernombudet har vurdert det til at den planlagte databehandlingen av personopplysninger / helseopplysninger tilfredsstiller de krav som stilles i helseforsknings- og personvernlovgivningen. Personvernombudet har ingen innvendinger til at den planlagte utleveringen av personopplysninger / helseopplysninger som kan utføreses under forutsetning av følgende:

1. Forskningsansvarlig / databehandlingsansvarlig er Oslo universitetssykehus HF ved adm. direktør.
2. Avdelingsleder og forskningsansvarlig i Gastrokirurgisk avdeling blir informert ved kopi av tilrådingen.
3. Studien er vurdert og godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK), og eventuelle merknader må følges.
4. Vedlagte pasientsamtykke er ifølge REK tilstrekkelig til å innhente informasjon fra eksterne.
5. Pasientopplysningene lagres som oppgitt i meldingen. Kodeliste som kobler avidentifiserte data (*indirekte identifiserbare helseopplysninger)* med personopplysninger lagres som angitt i meldingen og oppbevares separat nedlåst på adgangsbegrenset rom på sykehuset eller elektronisk som separat fil på tilgangsstyrt prosjektområde på forskningsserver med tilstrekkelige sikkerhetsinnretninger.
6. Behandling av personopplysningene / helseopplysninger (sensitive opplysninger) i prosjektet skjer i samsvar med og innenfor det formål som er oppgitt i meldingen og fremlagt dokumentasjon forøvrig.
7. Prosjektslutt er 31.03.2017. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2028 forutsatt overensstemmende med vedtak fra REK da skal data slettes eller anonymiseres ved at kodelisten slettes og eventuelle andre identifikasjonsmuligheter i databasen fjernes (senest 6 mnd etter sluttdato).
8. Dersom formålet, utvalget av inkluderte eller databehandlingen endres må tillatelse innhentes fra REK fra forskningsansvarlig.

Utleveringen er registrert i sykehusets offentlig tilgjengelig database over forsknings- og kvalitetsstudier.

Lykke til med studien!

Med vennlig hilsen
Personvernombud

Marianne B Blair
Akershus universitetssykehus HF

Epost: personvern@ahus.no
Web: www.ahus.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anette Solli Karlsen	22845522	16.09.2014	2013/1237/REK sør-øst A
			Deres dato:	**Deres referanse:**
			04.09.2014	

Vår referanse må oppgis ved alle henvendelser

Knut E. A. Lundin
Seksjon for gastromedisin, Oslo Universitetssykehus HF

2013/1237 Gluten provokasjon ved cøliaki og gluten sensitivitet

Forskningsansvarlig: Oslo Universitetssykehus HF
Prosjektleder: Knut E. A. Lundin

Vi viser til søknad om prosjektendring datert 04.09.2014 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
REK har vurdert følgende endringer i prosjekt:
-Endring i studiedesign. Prosjektet omfatter nå en 3-armet utprøving.
-Utvidelse av antall forskningsdeltakere: Det planlegges å inkludere 66 deltakere i prosjektet (tidligere godkjent 40).
-Innsamling av nytt biologisk materiale. Deltakere skal samle avføringsprøver ved 4 anledninger, disse skal inngå i prosjektets biobank og undersøkes for korte fettsyrer, pH, total bakterieforekomst og bakteriesammensetning.
-Forlenget provokasjonsperiode. Provokasjonsperioden forlenges fra 3 til 7 dager.
-revidert informasjonsskriv i forhold til endringer beskrevet ovenfor.

Komiteens leder har vurdert søknaden og har ingen innvendinger til de endringer som er beskrevet.

Vedtak
Komiteen godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

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

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding til REK, se helseforskningsloven § 12, senest 6 måneder etter at prosjektet er avsluttet.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf.

helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anette Solli Karlsen
Komitesekretær

Kopi til: *pline@ous-hf.no; oushfdlgodkjenning@ous-hf.no*

Generell forskningsbiobank

Tarmsykdommer

Prosjektbeskrivelse:
Formålet til forskningsgruppene som arbeider med tarmsykdommer ved Oslo Universitetssykehus Rikshospitalet er å; 1)kartlegge arvelige og miljømessige faktorer og forhold ved kroppens immunsystem som kan bidra til at tarmsykdommer oppstår og som kan være av betydning for forløpet av sykdommene og assosierte tilstander, og 2)forbedre diagnostikk og behandling av tarmsykdommer. Til slike studier vil vi ha behov for å bygge opp en biobank bestående av flere typer biologisk materiale. Totalt tre ulike forskningsgrupper vil i første omgang søke REK om prosjektgodkjenning for bruk av materialet i biobanken. Disse arbeider med dels ulike aspekter ved tarmsykdommmer og det er således ikke naturlig å søke om en prosjektbiobank. Det kan også finnes andre miljøer ved Oslo Universitetssykehus Rikshospitalet eller samarbeidende institusjoner som vil ha nytte av materialet i sin forskning.
(Redigert av REK)

Ref. nr.: 2012/341 Startdato for innsamling av materiale: 01.05.2012

Behandlingsstatus: Under behandling
Ansvarshavende: Knut E. A. Lundin
Forskningsansvarlig(e): Oslo Universitetssykehus Rikshospitalet
Finansieringskilder: Norsk senter for primær skleroserende cholangitt

Behandlet i REK

Dato	REK
15.03.2012	REK sør-øst
15.02.2017	REK sør-øst
15.02.2017	REK sør-øst

Utfylt av: GRY IRENE SKODJE (for GRY IRENE SKODJE)
Adresse: GRY IRENE SKODJE, HOVSETERVEIEN 64 B 0768 OSLO

Ny importør av næringsmidler

Her ser du en oppsummering av hva du har fylt inn i skjemaet - det er ikke innsendt ennå.

Du har registrert/meldt om nytt tilsynsobjekt av type Import av næringsmidler

Tilsynsobjekt: Import av næringsmidler

Generelle opplysninger om tilsynsobjektet

Navn på benyttet skjema	Ny importør av næringsmidler
Navn på tilsynsobjektet	Import av næringsmidler
Aktivitet	Import av næringsmidler
Beskrivelse	Muslibarer produsert ved Monash University i Melbourne, Australia, til bruk i klinisk studie på Rikshospitalet.
Kontaktperson	Gry Skodje

Detaljer om tilsynsobjektet

Importøren varsler også i Traces	Nei

Registrerte varegrupper

19042010	Musli-preparater på basis av ustekte flak av korn

Registrerte første mottakere

GRY IRENE SKODJE

Rikshospitalet – Radiumhospitalet HF

Medisinsk avdeling

Postadresse:
0027 OSLO

Besøksadresse:
Sognsvannsvn. 20

Sentralbord: 23 07 00 00
Dir. linje: 23 07 23 88
Telefaks: 23 07 24 10

knut.lundin
@rikshospitalet.no

Org.nr. NO 987 399 708 MVA

Rikshospitalet

Deres ref:
Vår ref:
Dato:

FORESPØRSEL OM DELTAGELSE I FORSKNINGSPROSJEKT GLUTENPROVOKASJON VED "USIKKER CØLIAKI" PASIENTINFORMASJON

Vi vil spørre deg om du vil delta i et forskningsprosjekt for å vurdere nytten av en blodprøve hos pasienter der cøliakidiagnosen er usikker. Deltakelse er helt frivillig.
For å vite om du kan delta i denne studien må du ha en spesiell vevstype som kalles DQ2, denne vevstypen finnes hos nesten alle med cøliaki, og hos ca 25% av den norske befolkningen. Vevstypen finner man ved å ta en vanlig blodprøve. Dersom du har denne vevstypen, kan du delta i studien.
Før du bestemmer deg om du vil delta, må du lese dette informasjonsskrivet nøye. Om du bestemmer deg for å delta i denne studien, må du signere på den vedlagte samtykkeerklæringen. Selv om du takker ja til å delta i studien, kan du når som helst trekke deg uten å oppgi noen grunn. Dette vil ikke få følger i forhold til dine rettigheter til utredning og behandling som du måtte ha i forhold til pasientrettighetsloven.

Bakgrunn: Cøliaki er en tynntarmsykdom der tarmtottene er skadet. Dermed blir tarmens evne til å oppta fødemidler redusert. Pasientene kan få diaré og symptomer som skyldes redusert opptak av jern, folsyre og kalk. Cøliaki utløses hos disponerte individer ved inntak av kornslag som hvete, rug og bygg. Man har lenge lett etter hvilke deler av hvete som er skadelig for tarmen, og vår forskningsgruppe har gjort flere avgjørende gjennombrudd. Vi vet i dag at sykdommen kommer i stand ved at immunapparatet reagerer på små protein biter (peptider) fra hvete gluten. Grunnpilaren i behandlingen av cøliaki er glutenfri diett. Når gluten ikke lenger inntas vil immunapparatet ikke lenger reagere, og betennelsen i slimhinnen gå tilbake. Et problem oppstår når cøliakipasienter begynner med glutenfri diett før diagnosen er sikker. Tarmen vil da bli normal og det er nødvendig med langvarig provokasjon med gluten for at tarmen igjen skal bli skadet og legen kan stille diagnosen basert på undersøkelsen av vevsprøver tatt fra tynntarmen under gastroskopi.

Hensikt med prosjektet: Å undersøke om det er mulig å finne sykdomsspesifikke celler i blod hos voksne pasienter med ”usikker cøliaki” etter at de har inntatt glutenholdige måltider. Vi håper at denne blodprøven i framtida kan bidra i diagnostikk av pasienter med ”usikker cøliaki”. Samtidig vil vi se etter forandringer i vevsprøver tatt fra tynntarmen og i tynntarmsfunksjonen målt ved pusteprøve.
Tidsrom: I løpet av 2006-2007
Metoder: Vi vil undersøke 50 pasienter med ”usikker cøliaki”. Det vil si pasienter som lever på glutenfri diett, uten å ha fått påvist cøliaki med vevsprøver fra tynntarm tatt under normalt kosthold. I tillegg vil vi undersøke 10 pasienter med kjent cøliaki som kontrollpersoner. Hos forsøkspersonene som samtykker i dette, gjør vi først en gastroskopi (”kikkertundersøkelse” av magesekk og øvre del av tynntarm) med taking av vevsprøver fra tynntarmen. Gastroskopiundersøkelsen oppleves ofte som litt ubehagelig, men er gjort på noen få minutter. Taking av vevsprøver medfører som regel ikke ekstra ubehag. En slik gastroskopi er rutine i diagnostikk av cøliaki. Når man tar vevsprøve fra tynntarmen kan det være en risiko for blødning, men denne er ansett som svært liten. Vi tar i denne sammenheng ikke vevsprøver fra pasienter med kjent blødningstendens eller som bruker blodfortynnende medisiner på en slik måte at det gir blødningsrisiko. Det er svært sjelden man får komplikasjoner etter en slik vevsprøvetaking.

Få uker etter dette vil forsøkspersonene spise fire skiver brød tre dager på rad. Bortsett fra disse brødskivene, vil man spise glutenfri kost som vanlig. Vi vil ta blodprøve like før dette og tre dager etter at pasienten har spist den siste porsjonen med brød. Blodprøvene vi tar vil så bli undersøkt med avanserte metoder for å lete etter effekter av glutenprovokasjonen. Vi vil også gjøre ny gastroskopi med taking av vevsprøver fra tynntarmen og ny pusteprøve Vi anser risikoen for den enkelte pasient i denne studien som meget liten. Glutenprovokasjon kan gi kortvarig ubehag for pasientene, slik som kan skje når en pasient med cøliaki får i seg mindre mengder gluten. Det er

imidlertid meget lite sannsynlig at disse negative effektene vil vare mer enn noen få dager.
I forbindelse med glutenprovokasjonen ber vi deg fylle ut et spørreskjema med registrering av fysiske og psykiske symptomer.
Om du skulle få respons på glutenprovokasjonen, i form av endringer i vevsprøver fra tynntarm eller påvisning av glutenspesifikke celler i blod, vil vi anbefale en videre provokasjon. En videre glutenprovokasjon bør vare 8 uker, dette tilsvarer det spesialavdelinger i fordøyelsessykdommer anbefaler. Etter denne blir det en ny gastroskopi.

Etiske og personverns aspekter: Studien er forelagt den regionale etiske komité, som er en helt uavhengig instans, og som ikke har innvendinger mot at studien gjennomføres. Det opprettes en såkalt forskningsbiobank ledet av dr.med. Knut E. A. Lundin. Om en forsøksperson skulle ønske å tilbakekalle samtykket kan vedkommende kreve det biologiske materialet destruert og å slette eller utlevere helse- og personopplysninger. Dette kan ikke gjøres om opplysningene allerede har inngått i vitenskaplige arbeider. En forsøksperson kan når som helst trekke seg fra studien, uten å begrunne dette nærmere. Dette vil ikke få konsekvenser for videre utredning og behandling i helsevesenet. Pasientkontakten vil bli registrert i sykehusets journalsystem. Etter studien planlegger vi å ta vare på det biologiske materialet i fem år med tanke på mulige oppfølgingsstudier. Forskerne i studien har taushetsplikt.

Økonomiske aspekter: Det legges ikke opp til å utbetale noe honorar til forsøkspersonene, men vi kan dekke reiseutgifter eller andre utgifter til studien. Ingen av legene som er involvert mottar noen form for honorar fra noe firma for studien.

Aktuelle telefonnumre:
Dr Margit Brottveit, gastromedisinsk avdeling, Ullevål universitetssykehus, tlf 22 11 85 92 (kontor), 957 65633(mobil). Dr. Knut E. A. Lundin, Medisinsk avdeling, Rikshospitalet,
Tel 23 07 23 88 (sentralbord), 23 07 24 00(gastrolab), 909 80325 (mobil).

SAMTYKKE-ERKLÆRING

Jeg har fått utlevert og lest den utdelte pasientinformasjon, og har fått muntlig informasjon om forsøket.

Jeg samtykker i å delta i forsøket. Jeg er klar over at mitt samtykke ikke hindrer meg i når som helst å trekke meg fra forsøket uten å oppgi grunn. Hvis jeg trekker meg fra forsøket vil dette ikke få noen konsekvenser for sykehusets oppfølging av min tilstand.

Oslo,

_____
Underskrift

Navn (blokkbokstaver):

Telefon (privat):
Telefon (arbeid):
Telefon (mobil):

Det attesteres at informasjon er gitt

Oslo,

_____
Underskrift (ansvarlig lege)

Forespørsel om deltakelse i forskningsprosjektet

"Glutenprovokasjon ved mistenkt glutensensitivitet uten cøliaki – en retrospektiv studie"

Bakgrunn
Dette er et spørsmål til deg om å delta i en forskningsstudie for å evaluere utredningsmetoden ved mistenkt glutensensitivitet uten cøliaki (NCGS). Gastromedisinsk poliklinikk og Seksjon for klinisk ernæring, Rikshospitalet har utredet pasienter med mistenkt NCGS ved hjelp av åpen glutenprovokasjon siden 2009. Det er en relativt ny utredning som brukes i liten grad på andre sykehus enn Rikshospitalet. Det er derfor behov for å gjøre en systematisk gjennomgang og evaluere metoden.
Hovedhensikent med studien er å evaluere åpen glutenprovokasjon ved mistenkt glutensensitivitet uten cøliaki utført ved Oslo Universitetssykehus (OUS) Rikshospitalet fra 2009 og fortløpende.
Du blir forespurt om deltakelse fordi du har blitt utredet med denne metoden på Rikshospitalet.
Leger og forskere ved OUS arbeider hele tiden for å forbedre forståelsen av årsaken til tarmsykdommer og for å forbedre diagnostikk og behandling av slike tilstander. Resultatene av forskningen kan gi oss verdifull kunnskap og forståelse av mekanismer som kan ha betydning for framtidig oppfølging og behandling av pasientene.

Hva innebærer studien?
Deltakelse i studien innebærer at du gir tillatelse til at vi kan bruke opplysninger fra din journal som omhandler utredningen av NCGS. Opplysningene som vil bli lagret er informasjon fra utredningen hos lege og klinisk ernæringsfysiolog og resultatene fra glutenprovokasjonen. Det vil også bli lagret blodprøvesvar og svar på gastroskopi dersom dette er utført.

Mulige fordeler og ulemper
Du vil ikke ha noen spesielle fordeler av studien, men erfaringer fra studien vil senere kunne hjelpe andre med samme diagnose.

Hva skjer med informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer/direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger. Opplysningene blir senest slettet i 2028.

Frivillig deltakelse
Det er frivillig å delta i studien. Dersom du ikke ønsker å delta, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for den videre behandlingen du får ved sykehuset.
Dersom du ønsker å delta, undertegner du samtykkeerklæringen på neste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling på sykehuset. Dersom du senere ønsker å trekke deg, kan du kontakte prosjektleder Knut Lundin på 23 07 24 00 eller 23 07 24 04.

Samtykke for deltakelse i studien:

"Glutenprovokasjon ved mistenkt glutensensitivitet uten cøliaki – en retrospektiv studie"

Jeg er villig til å delta i studien

_____
(Navn, blokkbokstaver, evt navnelapp)

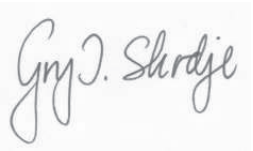
(Dato, signatur)

Bekreftelse på at informasjon er gitt deltakeren i studien

Jeg bekrefter å ha gitt informasjon om studien

Klinisk klinisk ernæringsfysiolog/stipendiat
Rikshospitalet, OUS

Klinisk ernæringsfysiolog
Ernæringspoliklinikken, OUS



(Signatur)

(Signatur)

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Oslo, 23.12.2013

Kreft-, kirurgi- og transplantasjonskl.
Avdeling for transplantasjonsmedisin
Seksjon for gastromedisin

Forespørsel om deltakelse i forskning
"Mekanismene for cøliaki – delprosjekt 14 dagers provokasjon med gluten"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i forskning for å øke kunnskapen om tynntarmsykdommer med spesielt fokus på cøliaki. Leger og forskere ved Oslo Universitetssykehus (OUS) arbeider hele tiden for å forbedre forståelsen av årsaken til tarmsykdommer og for å forbedre diagnostikk og behandling av slike tilstander. Resultatene av forskningen kan gi oss verdifull kunnskap og forståelse av mekanismer som kan ha betydning for framtidig oppfølging og behandling av pasientene.

Forløp studieplan:
I denne studien ønsker vi å undersøke hvor raskt totteforandringene kommer tilbake, etter at cøliakere re-introduserer gluten i kosten. Vi ønsker også å undersøke hvordan immunsystemet i tarmen aktiveres i løpet av en slik provokasjon. Studien innebærer at du spiser gluten i to uker. Du vil først snakke med studielegen og få nøye informasjon. Det vil bli tatt blodprøver ved første konsultasjon. Deretter skal det inntas glutenholdig brød daglig i to uker. Du vil få nærmere beskjed om hvilken type brød du skal spise, bortsett fra dette inntas glutenfri kost som før. Det vil bli tatt blodprøver også etter at du har spist gluten. Du må regne med ubehag mens du spiser gluten, dette er vanligvis forbigående og du vil få informasjon om hvordan du skal forholde deg til symptomer under studien. Cøliakere med kraftig reaksjon på gluten bør ikke delta i studien, dette vil bli tatt opp i samtalen med studielegene. Det er ønskelig å utføre gastroskopi før og etter provokasjon med gluten, men det er mulig å delta i studien også uten å stille til gastroskopi. Alle prosedyere blir utført på OUS Rikshospitalet av studielegene. Alle deltagere får informasjon om timeplanen i studien, og det er selvsagt frivillig å delta. Man kan også trekke seg mens studien pågår, uten å oppgi grunn, men studielegene vil bistå med medisinsk hjelp og råd.

Hva innebærer deltakelse i studiene?
I forbindelse med dette prosjektet er det nødvendig å ta prøver av blod, avføring og vevsprøver fra tarmene. Den aktuelle studie med 14 dagers provokasjon med gluten er nært knyttet til vår øvrige cøliakiforskning, og alt biologisk materiale fra denne studien kan komme til nytte i våre øvrige prosjekter. Vi spør deg derfor om du vil gi tillatelse til:

- at deler av prøvene som blir til overs kan oppbevares til senere bruk i forskning på tarmsykdommer som ledd i vår overordnede studie "Immunologisk basis for cøliaki".
- at blod- og/eller vevsprøver som allerede finnes ved OUS laboratorier, tatt i forbindelse med tidligere undersøkelser og behandling eller forskningsprosjekt, også kan benyttes i forskningen
- å ta blodprøver til studier av arvestoff (gener) og andre komponenter av mulig betydning for utvikling av tarmsykdom
- å ta vevsprøver fra tarmslimhinnen,

Mulige fordeler og ulemper
Resultatene av forskningen vil som hovedregel ikke ha direkte betydning for din behandling på det nåværende tidspunkt, men de vil danne grunnlag for bedre behandlingstilbud for pasienter med tarmsykdommer som cøliaki i framtiden. Dette kan også komme deg til nytte. All informasjon av

medisinsk relevans som fremkommer som ledd i forskningen, vil bli vurdert av prosjektleder og klinikerne som deltar i forskningen. Der det er klinisk grunn til det, vil du bli kontaktet for å drøfte funnene. Du kan også få tilgang til resultatet av prøver som er utført på ditt biologiske materiale ved å kontakte prosjektleder.
Mulige ulemper knyttet til glutenprovokasjon og undersøkelser er beskrevet under kapittel A.

Frivillig deltakelse
Det er frivillig å delta i studiene. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta. Dette vil ikke få konsekvenser for din videre behandling fra sykehusets side. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Dersom du senere ønsker å trekke deg eller har spørsmål til studiene, kan du kontakte overlege, dr. med. Knut E. A. Lundin, Gastro undersøkelse. OUS Rikshospitalet, tlf. 23 07 23 88, 2307 24 00 el. 23 07 00 00.

Ytterligere informasjon om studiene finnes i kapittel *A* – *utdypende forklaring av hva studiene innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Oslo universitetssykehus

Kapittel A- utdypende forklaring om deltakelse i forskning

Hvem blir forespurt om å delta i forskning påen
Pasienter som er henvist til OUS, eller samarbeidende sykehus, til utredning og/eller behandling for tarmsykdommer inkludert, men ikke begrenset til, tynntarmsykdommen cøliaki og deres nære slektninger kan bli forespurt om å gi sitt samtykke til deltakelse i studiene. Det er også aktuelt å inkludere frivillige cøliakere eller andre personer, som ønsker å bidra til forskning.

Bakgrunnsinformasjon om studiene
Årsaken til cøliaki er bare delvis kjent. Hos pasienter med cøliaki skjer det en immunreaksjon mot gluten, et protein som finnes i hvete, spelt, rug og bygg. Så lenge pasientene spiser skadelige kornslag, gjør betennelsen at tarmtottene er borte, og opptaket av næring og vitaminer fra tarmen reduseres. Pasientene merker dette med magesmerter, urolig mage, mange har diaré, og de fleste føler tretthet. Noen pasienter med aktiv cøliaki opplever seg som friske, men det er da vanlig at de allikevel føler seg enda bedre når de starter med gluten fri kost. Når pasientene med cøliaki slutter å spise skadelige kornslag går betennelsen tilbake og tottene vokser ut igjen. Mange pasienter som reagerer på gluten eller annen mat gjør det uten de typiske cøliakiforandringene i tarmen. Man snakker da gjerne om "non-cøliakisk gluten sensitivitet". Gener er av betydning for utviklingen av sykdommene, men andre faktorer spiller også en viktig rolle. Vi ønsker å kartlegge videre hvilke gener som kan bidra til utvikling og forløp av cøliaki og hvordan gener kan samspille med immunsystemet eller andre faktorer. Økt forståelse av sykdomsmekanismene kan gi grunnlag for bedre oppfølging og behandling av pasienter med slike sykdommer.

I studiene er vi ofte interesserte i vevsprøver fra personer som ikke har cøliaki. Dette vil være personer som kommer til undersøkelse enten på grunn av andre, kjente sykdomstilstander, eller der man ønsker å utelukke sykdom. Slike personer er svært verdifulle for studiene fordi vi da sammenligner immunsystemet hos cøliakere med immunsystemet hos andre.

Noen ganske få pasienter med cøliaki utvikler komplikasjoner i form av forstadier til kreft eller kreft i tarmen eller lymfesystem. Vi vil arbeide med å utvikle metoder for å kunne påvise tidlige stadier av kreft, slik at behandling kan iverksettes så tidlig som mulig.

Prøver fra blod, afføring og vev
Blodprøver vil bli tatt 5 ganger i løpet av studien. Den totale mengde blod vil tilsvare det som vanligvis blir tatt ved blodgiving til blodbanken (ca. 400 ml). Hvis det foreligger kjent blodmangel, eller hvis dette oppdages ved første blodprøve, vil man vurdere forsvarligheten av ytterligere blodtaking og evt. redusere på mengden blod som tas hvis blodmangelen er mild/moderat.
Det planlegges taking av avføringsprøver med tilrettelagt oppsamlingsutstyr.
Vevsprøver tas ved gastroskopi.

Prøvene fra deg vil enten bli lagret i fryseboks eller vi vil straks prosessere dem videre. Vår laboratorieaktivitet favner nær sagt alle metoder innen moderne, bioteknologisk forskning. Dette innbefatter:

- Undersøkelse av celler og signalstoffer i vevsprøver, blod og serum
- Dyrkning av dine immunceller i reagensrør og undersøkelse på deres funksjon og

reaksjonsmønster
- Undersøkelse av hvilke gener som er skrudd på i vevsprøver og i blodceller
- Isolering av enkelte gener hos den enkelte pasient og undersøkelse på hvilke varianter de har
- Undersøkelse av hele arvematerialet hos pasientene for å forstå samspillet mellom de enkelte genene

Mulige ubehag/ulemper
Deltakelse i studiene kan medføre ekstra ubehag og ulempe for deg. Du vil bli spurt om å spise mat som du kan reagere på. Dette er en vanlig prosedyre ved utredning av matvareintoleranse og cøliaki. Noen personer kan oppleve symptomer som kvalme, oppkast, slapphet og diare. Vi ønsker derfor kun å inkludere personer som ikke har en historie med sterk reaksjon på gluten. Som en ekstra sikkerhet vil den første dosen med gluten bli gitt på sykehus med mulighet for raskt tilsyn av lege i timene etter inntak.
Som ledd i denne studien vil du gjennomgå en gastroskopi. Dette er en undersøkelse du sannsynligvis kjenner godt fra før. Man fører da en slange med kamera på tuppen for å undersøke slimhinnen i tarmen, og via et rørsystem kan man også ta små vevsprøver. De fleste opplever denne undersøkelsen som noe ubehagelig da man under undersøkelsen vil kunne oppleve brekninger, luftsmerter i magen og noen vil også kunne få følelse av angst. Undersøkelsen er ufarlig da komplikasjonsraten er svært lav i trenede hender. Ved OUS Rikshospitalet er det personell med lang erfaring innen dette og det foreligger også tilbud om beroligende medisin før undersøkelsen.
Alle prosedyrene utføres av spesialtrenet personell som vil legge stor vekt på å minimalisere ubehaget for den enkelte deltager. Det blir ikke tatt prøver hvis man mistenker at dette kan gå utover pasientenes sikkerhet eller hvis pasienten er uvanlig besværet under prøvetakingen.

Man kan tenke seg at det i studien gjøres funn som har klinisk betydning for den enkelte pasient. Dette kan for eksempel innebære at man finner tegn til ondartet sykdom (kreft). Slike opplysninger vil uten unntak bli vurdert av prosjektleder etter at de er spilt inn fra forskerne i studien. Dagens vitenskapelige metoder innbefatter analyse på enkeltgener hos den enkelte pasient. Selv om vi planlegger all vår forskning slik at den ikke skal fange opp såkalte "sykdomsgener", kan man ikke helt garantere at dette kan skje. Vi har allerede etablert en beredskap for slike tilfeller. Vi har avtalt med spesialist i medisinsk genetikk, som vil rådgi prosjektleder og ta seg av informasjon til den enkelte pasient. Dette er i henhold til gjeldende regelverk og lovgivning.

Ny informasjon som kan påvirke studiene
Dersom ny informasjon blir tilgjengelig som kan påvirke din villighet til å delta i studiene, vil du bli orientert så raskt som mulig.

Kapittel B - Personvern, biobank, økonomi og forsikring

Hva skjer med prøvene og informasjonen om deg?

Kodenummer
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i denne informasjonen. Prøvene blir merket med et kodenummer og vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Listen som knytter ditt navn til kodenummeret vil bli oppbevart separat. Det er kun autorisert, sentralt personell (leger eller annet personell med taushetsplikt) knyttet til forskningsprosjektene som har adgang til navnelisten og som kan finne tilbake til deg.

Det vil ikke være mulig å identifisere deg i resultatene av studiene når disse publiseres.

Personvern
Opplysninger som registreres om deg vil gjelde forhold som vi mener kan være av betydning for utvikling og forløp av din tarmsykdom. Dette vil også inkludere andre tilstander som av og til ses samtidig med tarmsykdommer. Vi vil registrere symptomer, blodprøvesvar, funn ved andre typer undersøkelser (for eksempel røntgenundersøkelser) og behandling som er gitt. Vi vil primært benytte opplysninger fra din journal ved OUS. Av og til vil det være nødvendig å innhente supplerende opplysninger av tilsvarende type fra journal hos fastlege eller annen helseinstitusjon.

I enkelte prosjekter kan det bli aktuelt å koble forskningsdata til andre registre. Slik kobling vil bare skje etter forutgående godkjenning av Datatilsynet og Regional etisk komité for medisinsk og helsefaglig forskningsetikk. Opplysninger fra aktuelle registre omfatter: eventuell kreftforekomst (Kreftregisteret), dødsårsak (Dødsårsaksregisteret), medisinske forhold rundt fødsel (Medisinsk fødselsregister), medikamenter (Reseptregisteret) og bosted (Folkeregisteret). Alle data lagres i henhold til prosedyrer som er godkjent av Personvernombudet.

Oslo Universitetssykehus ved administrerende direktør er databehandlingsansvarlig.

Biobank
Prøver fra blod, andre vevsvæsker og vev og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved OUS. Hvis du sier ja til å delta i studiene, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Biobanken er tilrådd av Regional etisk komité for medisinsk og helsefaglig forskningsetikk, og godkjent av Helsedirektoratet. Biobanken drives i tråd med nasjonale og lokale retningslinjer. Overlege, dr. med. Knut E. A. Lundin er ansvarshavende for forskningsbiobanken. Biobanken og helseopplysningene planlegges å lagres i første omgang til 2028. Det kan bli aktuelt å søke om forlenget oppbevaring, og vi ber derfor om å kunne komme tilbake for å be om slik forlengelse. Når forskningsprosjektet avsluttes, vil materiale og opplysninger bli destruert og slettet etter interne retningslinjer.

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studiene, gir du også ditt samtykke til at prøver og avidentifiserte

opplysninger utleveres til forskningsgrupper vi samarbeider med. Vi samarbeider i størst utstrekning med forskningsgrupper innen EU, men samarbeidet kan også gjelde land med lover som ikke tilfredsstiller europeisk personvernlovgivning.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studiene, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studiene, kan du kreve å få slettet innsamlede prøver og opplysninger. Opplysninger som allerede er publisert kan imidlertid ikke slettes fra eventuelle publikasjoner. Det samme gjelder gensekvenser, cellelinjer eller annet biologisk materiale som er laget på basis av de prøvene du har avgitt. Eiendomsretten til disse bearbeidete produktene vil tilfalle forskerne i prosjektet, etter de regler som er gjeldende innenfor OUS og Universitet i Oslo. Det er et uttrykt mål at eventuelle oppfinnelser innen medisinsk vitenskap skal patenteres. Dette fordi de da kan kommersialiseres og bidra til nye behandlingsmåter utviklet av legemiddelindustri. Eiendomsretten til slik oppfinnelser tilfaller oppfinnerne/forskerne, og affiseres ikke av at du trekker din individuelle godkjenning tilbake. All vitenskapelig virksomhet i prosjektet kan selvsagt bli gjenstand for offentlig ettersyn.

Sensitive opplysninger
Alle forhold rundt en pasients helse er sensitive opplysninger. Håndtering av slike opplysninger er vel regulert av lovverket og interne retningslinjer.

Økonomi
Prosjektet og biobanken er finansiert gjennom offentlige forskningsmidler. Slike midler tilføres forskningsgruppen fra Universitetet i Oslo, fra Helse Sør-Øst, fra EUs forskningsprogram, fra National Institute of Health, fra stiftelsen Helse og Rehabilitering, fra forskningsstiftelsen Inven2 og fra en rekke andre finansieringskilder.

Forsikring
Du har vanlige pasientrettigheter som ledd i din kontakt med helseinstitusjonen og eventuell søknad til Norsk pasientskadeerstatning kan sendes på vanlig måte. Det er ingen spesiell forsikring knyttet til prosjektene.

Informasjon om utfallet av studiene
Deltakerne har rett til å få informasjon om resultatene av studiene som utføres. I hovedsak vil resultatene bli tilgjengelige som publikasjoner i internasjonale vitenskapelige tidsskrift.

Samtykke til deltakelse i studien *"Mekanismene for cøliaki – delprosjekt 14 dager provokasjon med gluten"*

Navnelapp eller navn med blokkbokstaver og fødselsdato:

Jeg er villig til å delta i studiene "Mekanismene for cøliaki".

(Signert av prosjektdeltaker, dato)

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

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(Signert av nærstående, dato)

Jeg bekrefter å ha gitt informasjon om studiene

(Signert, medlem av prosjektledelsen, dato)

Forespørsel om deltakelse i forskningsprosjektet

Delstudie til "Glutenprovokasjon ved cøliaki og glutensensitivitet uten cøliaki"

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

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke effekten av gluten og andre kostholdsfaktorer ved glutensensitivitet uten cøliaki. Leger og forskere ved Oslo Universitetssykehus (OUS) arbeider hele tiden for å forbedre forståelsen av årsaken til tarmsykdommer og for å forbedre diagnostikk og behandling av slike tilstander. Resultatene av forskningen kan gi oss verdifull kunnskap og forståelse av mekanismer som kan ha betydning for framtidig oppfølging og behandling av pasientene.

Studiens forløp
I denne studien ønsker vi å undersøke i hvilken grad det er gluten eller såkalte kortkjedete karbohydrater (FODMAP= Fermentable Oligo- Di- Monosaccharides And Polyols) som er årsaken til plager hos pasienter med mistenkt glutensensitivitet uten cøliaki. Du vil bli tilfeldig valgt ut til å spise en müslibar som inneholder enten gluten, FODMAP eller narremiddel (placebo) i 7 dager – en såkalt matvareprovokasjon. Verken du eller forskeren vet hvilken type du får. Dette skjer tre ganger fordi hver deltaker skal spise gluten i en uke, FODMAP i en uke og placebo i en uke. Vi ønsker å undersøke plagene som oppstår ved inntak av de ulike müslibarene. Du vil derfor bli bedt om å fylle ut spørreskjemaer som handler om blant annet mage- og tarmplager, livskvalitet og konsentrasjonsevne ved hver av de tre provokasjonene. Mellom hver provokasjon får du omtrent en ukes pause før neste provokasjon. Bortsett fra müslibaren skal du spise ditt vanlige glutenfrie kosthold. Vi ønsker at du tar en avføringsprøve før du starter og ved slutten av hver provokasjonsperiode, i alt seks prøver. Du vil få instruksjon og nødvendig utstyr til å ta disse hjemme.
Før du starter får du grundig informasjon i samtale med studielegen og klinisk ernæringsfysiolog. Her vil vi også gjøre en gastroskopiundersøkelse og ta vevsprøver fra tynntarmen. Det vil bli tatt blodprøver ved første konsultasjon, og deretter på første dag av hver provokasjonsuke.
Alle prosedyrer blir utført på OUS Rikshospitalet av spesialtrenet personell. Alle deltagere får informasjon om timeplanen i studien, og det er selvsagt frivillig å delta. Man kan også trekke seg mens studien pågår, uten å oppgi grunn, men studielegene vil bistå med medisinsk hjelp og råd.

Hva innebærer deltakelse i studien?
I forbindelse med dette prosjektet er det nødvendig å ta prøver av blod, vevsprøver og avføring. Den aktuelle studien er nært knyttet til vår øvrige cøliakiforskning, og alt biologisk materiale fra denne studien kan komme til nytte i våre øvrige prosjekter. Vi spør deg derfor om du vil gi tillatelse til:

- undersøker celler og signalstoffer i vevsprøver, blod og serum
- at deler av prøvene som blir til overs kan oppbevares til senere bruk i forskning på tarmsykdommer
- å ta ekstra blodprøver til studier av arvestoff (gener) og andre komponenter av mulig betydning for utvikling av tarmsykdom
- å fylle ut spørreskjemaer for å kartlegge symptomer før, under og etter matvareprovokasjon

Mulige fordeler og ulemper
Resultatene av din individuelle provokasjonsperiode vil kunne gi deg direkte informasjon om din tilstand slik at du får tilpasset medisinsk behandling og kostholdsveiledning. Forskningsresultatene vil danne grunnlag for bedre utredning og behandlingstilbud for pasienter mistenkt glutensensitivitet uten cøliaki i nær framtid. All informasjon av medisinsk relevans som fremkommer som ledd i forskningen, vil bli vurdert av prosjektleder og klinikerne som deltar i forskningen. Der det er klinisk grunn til det, vil du bli kontaktet for å drøfte funnene. Du kan også få tilgang til resultatet av prøver som er utført på ditt biologiske materiale ved å kontakte prosjektleder.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste.
Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studiene. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta. Dette vil ikke få konsekvenser for din videre behandling fra sykehusets side. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Dersom du senere ønsker å trekke deg eller har spørsmål til studiene, kan du kontakte overlege, dr. med. Knut E. A. Lundin, Gastroundersøkelse. OUS Rikshospitalet, tlf. 23 07 23 88, 2307 24 00 el. 23 07 00 00.

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Hvem blir forespurt om å delta i forskningsstudien?
Pasienter som er henvist til OUS, eller samarbeidende sykehus, til utredning og/eller behandling for glutensensitivitet uten cøliaki kan bli forespurt om å gi sitt samtykke til deltakelse i studien. Invitasjonen går også ut til publikum der kriteriet for å delta er at cøliaki er utelukket ved gastroskopi med tynntarmsbiopsi. Hveteallergi skal også være utelukket. Personer som kan delta skal ha oppnådd symptomlindring på konsekvent glutenfri kost.

Bakgrunnsinformasjon om studien
Et ukjent antall i befolkningen har ikke cøliaki, men tåler likevel ikke gluten i kosten. Tilstanden er definert som en klinisk tilstand der gluten i kosten gir symptomer som ligner på cøliaki, men der man ikke finner tegn til cøliaki verken med blodprøver eller etter gastroskopi med biopsi. Årsakssammenhengen er uklar og man har ingen god definisjon på sykdommen. Tilstanden har vært kjent i flere år, men utbredelsen har økt de siste få årene. Mange kommer til spesialisthelsetjenesten for å få hjelp, og selv der er utredningen er utfordrende. Det er fortsatt usikkert om det er gluten som gir symptomer. Noe forskning peker mot de såkalte FODMAP som en forklaring på plagene. Målet med studien er å øke kunnskapen om glutensensitivitet uten cøliaki ved å undersøke betydningen av gluten og FODMAP i kostholdet. Vi ønsker også å forbedre utredningsmetoden.

Prøver fra vev og vevsvæsker, blod og avføring
Ved gastroskopi vil det bli tatt vevsprøver fra tynntarm. Disse vil bli brukt til å vurdere betennelsesmarkører i tynntarmen. Det vil bli tatt blodprøver ved fire anledninger i løpet av studien. Du vil også bli bedt om å ta avføringsprøver seks ganger. Dette tas for å undersøke hvordan immunsystemet og tarmens bakterieflora reagerer på inntaket av det du blir bedt om å spise.

Mulige fordeler
En åpenbar fordel for deg som deltar er at du får en grundig utredning av din tilstand som vil gi svar på hva som vil være den beste behandlingen for deg. Som deltaker er det viktig at du rapporterer hvordan du har det så sant som mulig i spørreskjemaene. Det er også viktig at du melder fra dersom du ikke får til å følge studieplanen slik som planlagt. Dersom du skulle velge ikke å delta i studien vil du få tilbud om standard behandling.

Mulige ubehag/ulemper
Deltakelse i studien kan medføre ekstra ubehag og ulempe for deg i deler av forløpet. I dette tilfellet ønsker vi at du skal spise mat (gluten) som du kan reagere på, dette er en vanlig prosedyre ved utredning av matvareintoleranse. Det kan gi ubehag, men det er ingen risiko forbundet med å delta. Dersom gluten gir alvorlige reaksjoner, skal du ikke delta.
Som ledd i denne studien vil du gjennomgå en gastroskopi. Dette er en undersøkelse du sannsynligvis kjenner godt fra før. Man fører da en slange med kamera på tuppen for å undersøke slimhinnen i tarmen, og via et rørsystem kan man også ta små vevsprøver. De fleste opplever denne undersøkelsen som noe ubehagelig da man under undersøkelsen vil kunne oppleve brekninger, luftsmerter i magen og noen vil også kunne få følelse av angst. Undersøkelsen er ufarlig da komplikasjonsraten og blødningsrisikoen er svært lav i trenede hender. Ved OUS Rikshospitalet er det personell med lang erfaring innen dette og det foreligger også tilbud om beroligende medisin før undersøkelsen.
Alle prosedyrene utføres av spesialtrenet personell som vil legge stor vekt på å minimalisere ubehaget for den enkelte deltager. Det blir ikke tatt prøver hvis man mistenker at dette kan gå utover pasientenes sikkerhet eller hvis pasienten er uvanlig besværet under prøvetakingen.

Man kan tenke seg at det i studien gjøres funn som har klinisk betydning for den enkelte pasient. Dette kan for eksempel innebære at man finner tegn til ondartet sykdom (kreft). Slike opplysninger vil uten unntak bli vurdert av prosjektleder etter at de er spilt inn fra forskerne i studien. Dagens vitenskapelige metoder innbefatter analyse på enkeltgener hos den enkelte pasient. Selv om vi planlegger all vår forskning slik at den ikke skal fange opp såkalte "sykdomsgener", kan man ikke helt garantere at dette kan skje. Vi har allerede etablert en beredskap for slike tilfeller. Vi har avtalt med spesialist i medisinsk genetikk, som vil rådgi prosjektleder og ta seg av informasjon til den enkelte pasient. Dette er i henhold til gjeldende regelverk og lovgivning.

Ny informasjon som kan påvirke studiene
Dersom ny informasjon blir tilgjengelig som kan påvirke din villighet til å delta i studiene, vil du bli orientert så raskt som mulig.

Kapittel B - Personvern, biobank, økonomi og forsikring

Hva skjer med prøvene og informasjonen om deg?

Kodenummer
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i denne informasjonen. Prøvene blir merket med et kodenummer og vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Listen som knytter ditt navn til kodenummeret vil bli oppbevart separat. Det er kun autorisert, sentralt personell (leger eller annet personell med taushetsplikt) knyttet til forskningsprosjektene som har adgang til navnelisten og som kan finne tilbake til deg.

Det vil ikke være mulig å identifisere deg i resultatene av studiene når disse publiseres.

Personvern
Opplysninger som registreres om deg vil gjelde forhold som vi mener kan være av betydning for utvikling og forløp av din tarmsykdom. Dette vil også inkludere andre tilstander som av og til ses samtidig med tarmsykdommer. Vi vil registrere symptomer, blodprøvesvar, funn ved andre typer undersøkelser (for eksempel røntgenundersøkelser) og behandling som er gitt. Vi vil primært benytte opplysninger fra din journal ved OUS. Av og til vil det være nødvendig å innhente supplerende opplysninger av tilsvarende type fra journal hos fastlege eller annen helseinstitusjon.

I enkelte prosjekter kan det bli aktuelt å koble forskningsdata til andre registre. Slik kobling vil bare skje etter forutgående godkjenning av Datatilsynet og Regional etisk komité for medisinsk og helsefaglig forskningsetikk. Opplysninger fra aktuelle registre omfatter: eventuell kreftforekomst (Kreftregisteret), dødsårsak (Dødsårsaksregisteret), medisinske forhold rundt fødsel (Medisinsk fødselsregister), medikamenter (Reseptregisteret) og bosted (Folkeregisteret). Alle data lagres i henhold til prosedyrer som er godkjent av Personvernombudet.

Oslo Universitetssykehus ved administrerende direktør er databehandlingsansvarlig.

Biobank
Prøver fra blod, andre vevsvæsker og vev og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved OUS. Hvis du sier ja til å delta i studiene, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Biobanken er tilrådd av Regional etisk

komité for medisinsk og helsefaglig forskningsetikk, og godkjent av Helsedirektoratet. Biobanken drives i tråd med nasjonale og lokale retningslinjer. Overlege, dr. med. Knut E. A. Lundin er ansvarshavende for forskningsbiobanken. Biobanken og helseopplysningene planlegges å lagres i første omgang til 2028. Det kan bli aktuelt å søke om forlenget oppbevaring, og vi ber derfor om å kunne komme tilbake for å be om slik forlengelse. Når forskningsprosjektet avsluttes, vil materiale og opplysninger bli destruert og slettet etter interne retningslinjer.

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studiene, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til forskningsgrupper vi samarbeider med. Vi samarbeider i størst utstrekning med forskningsgrupper innen EU, men samarbeidet kan også gjelde land med lover som ikke tilfredsstiller europeisk personvernlovgivning.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studiene, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studiene, kan du kreve å få slettet innsamlede prøver og opplysninger. Opplysninger som allerede er publisert kan imidlertid ikke slettes fra eventuelle publikasjoner. Det samme gjelder gensekvenser, cellelinjer eller annet biologisk materiale som er laget på basis av de prøvene du har avgitt. Eiendomsretten til disse bearbeidete produktene vil tilfalle forskerne i prosjektet, etter de regler som er gjeldende innenfor OUS og Universitet i Oslo. Det er et uttrykt mål at eventuelle oppfinnelser innen medisinsk vitenskap skal patenteres. Dette fordi de da kan kommersialiseres og bidra til nye behandlingsmåter utviklet av legemiddelindustri. Eiendomsretten til slik oppfinnelser tilfaller oppfinnerne/forskerne, og affiseres ikke av at du trekker din individuelle godkjenning tilbake. All vitenskapelig virksomhet i prosjektet kan selvsagt bli gjenstand for offentlig ettersyn.

Sensitive opplysninger
Alle forhold rundt en pasients helse er sensitive opplysninger. Håndtering av slike opplysninger er vel regulert av lovverket og interne retningslinjer.

Økonomi
Prosjektet og biobanken er finansiert gjennom offentlige forskningsmidler. Slike midler tilføres forskningsgruppen fra Universitetet i Oslo, fra Helse Sør-Øst, fra EUs forskningsprogram, fra National Institute of Health, fra stiftelsen Helse og Rehabilitering, fra forskningsstiftelsen Inven2 og fra en rekke andre finansieringskilder.

Forsikring
Du har vanlige pasientrettigheter som ledd i din kontakt med helseinstitusjonen og eventuell søknad til Norsk pasientskadeerstatning kan sendes på vanlig måte. Det er ingen spesiell forsikring knyttet til prosjektene.

Informasjon om utfallet av studiene
Deltakerne har rett til å få informasjon om resultatene av studiene som utføres. I hovedsak vil resultatene bli tilgjengelige som publikasjoner i internasjonale vitenskapelige tidsskrift.

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

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(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)

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 brødsmuler?

☐ 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

Deltaker ID_____

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 *ikke*-glutensensitive?

☐ Mye bedre ☐ Litt bedre ☐ Like god ☐ Litt dårligere ☐ Mye dårligere

Deltaker ID_____

Test for etterlevelse av glutenfri kost[1]

Sett ring rundt svaralternativet som passer best:

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

[1] Celiac Dietary Adherence Test (CDAT) The Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA. Leffler D, Dennis M, Edwards George J, Jamma S, Magge S, Cook EF, Schuppan D, Kelly CP. A Simple Validated Gluten Free Diet Adherence Survey for Adults with Celiac Disease. Clinical Gastroenterology and Hepatology. 2009 May;7(5):530-6, 536.e1-2. Epub 2009 Jan 11.

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: _____

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

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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

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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

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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)?

- ☐ 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

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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.

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Cøliakispesifikk Symptom Indeks (CSI)[1]

Spørsmål	1	2	3	4	5
1. Har du vært plaget med smerte eller ubehag i øvre eller sentrale del av magen i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
2. Har du vært plaget med kvalme i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
3. Har du vært plaget med rumling i magen i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
4. Har du vært oppblåst i magen i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
5. Har du vært plaget med diaré i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
6. Har du hatt følelsen av ufullstendig tømming når du har vært på toilettet i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
7. Har du vært plaget med sultsmerter i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
8. Har du vært plaget av manglende overskudd i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
9. Har du vært plaget av hodepine i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
10. Har du fyset på spesiell mat i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
11. Har du hatt manglende matlyst i løpet av de siste 4 ukene?	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mesteparten av tiden	Hele tiden
12. Relatert til din cøliaki, hvordan er helsen din?	Utmerket	God	Ganske god	Dårlig	Meget dårlig
13. Generelt sett, hvordan er helsen din?	Utmerket	God	Ganske god	Dårlig	Meget dårlig
14. Hvor mye fysisk smerte har du hatt i løpet av de siste 4 ukene?	Ingenting	Litt	En del	Ganske mye	Veldig mye
15. Jeg har det (helsemessig) bra	Sterkt enig	Noe enig	Verken enig eller uenig	Noe uenig	Sterkt uenig
16. Jeg er like frisk som hvem som helst andre jeg kjenner	Sterkt enig	Noe enig	Verken enig eller uenig	Noe uenig	Sterkt uenig

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:_____

Jeg føler meg belastet med følgende plager.

1. **Slapphet/svakhet**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

2. **Overdrevent søvnbehov**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

3. **Fort sliten/utmattet**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

4. **Tretthet**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

5. **Følelse av å være "utenfor" eller fortumlet**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

6. **Følelse av utmattelse**
   ☐ Ikke ☐ Muligens litt ☐ Noe ☐ Betydelig ☐ Sterkt

Deltaker ID_____

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

Dato:_____

Lite slapp/svak _____ Mye slapp/svak

Lite plaget av overdrevent søvnbehov _____ Mye plaget av overdreven søvnbehov

Lite plaget av fort sliten/utmattet _____ Mye plaget av fort sliten/utmattet

Lite trett _____ Mye trett

Lite "utenfor" eller fortumlet _____ Mye "utenfor" eller fortumlet

Lite utmattet _____ Mye utmattet

Lite følelse av nummenhet i hender og føtter _____ Mye følelse av nummenhet i hender og føtter

Lite følelse av prikking i hender og føtter _____ Mye følelse av prikking i hender og føtter

Lite opplevelse av manglende fokus (konsentrasjon) _____ Mye opplevelse av manglende fokus (konsentrasjon)

Lite ledd og muskelsmerter _____ Mye ledd og muskelsmerter

Lite deprimert _____ Veldig deprimert

Deltaker ID_____

Rikshospitalet – Radiumhospitalet HF

Versjon: Baseline

Dato: ..

Deltaker ID

HAD

Dette spørreskjemaet er laget for å hjelpe oss til å forstå hvordan du føler deg. Les hver linje og marker i boksen for det svar som beskriver dine følelser DEN SISTE UKEN.

1. Jeg er nervøs eller anspent

- ☐ For det meste
- ☐ Ofte
- ☐ Noen ganger
- ☐ Ikke i det hele tatt

2. Jeg gleder meg fremdeles over ting jeg pleide å glede meg over

- ☐ Avgjort like mye
- ☐ Ikke fullt så mye
- ☐ Bare litte grann
- ☐ Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig kommer til å skje

- ☐ Helt sikkert og svært ille
- ☐ Ja, men ikke så veldig ille
- ☐ Litt ille, men det bekymrer meg ikke så mye
- ☐ Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner

- ☐ Like mye som jeg alltid har gjort
- ☐ Ikke like mye nå som før
- ☐ Avgjort ikke så mye nå som før
- ☐ Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer

- ☐ Veldig ofte
- ☐ Ganske ofte
- ☐ Av og til
- ☐ En gang i blant

6. Jeg er i godt humør

- ☐ Aldri
- ☐ Noen ganger
- ☐ Ganske ofte
- ☐ For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet

- ☐ Ja, helt klart
- ☐ Vanligvis
- ☐ Ikke så ofte
- ☐ Ikke i det hele tatt

8. Jeg føler det som om alt går langsommere

- ☐ Nesten hele tiden
- ☐ Svært ofte
- ☐ Fra tid til annen
- ☐ Ikke i det hele tatt

9. Jeg føler meg urolig liksom jeg har sommerfugler i magen

- ☐ Ikke i det hele tatt
- ☐ Fra tid til annen
- ☐ Ganske ofte
- ☐ Svært ofte

10. Jeg har sluttet å bry meg om hvordan jeg ser ut

- ☐ Ja, helt klart
- ☐ Jeg bryr meg ikke så mye som jeg burde
- ☐ Det kan nok hende at jeg ikke bryr meg nok
- ☐ Jeg bryr meg om utseendet like mye som jeg alltid har gjort

11. Jeg føler meg rastløs som om jeg stadig må være i aktivitet

- ☐ Uten tvil svært mye
- ☐ Ganske mye
- ☐ Ikke så veldig mye
- ☐ Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

- ☐ Like mye som jeg alltid har gjort
- ☐ Heller mindre enn jeg pleier
- ☐ Avgjort mindre enn jeg pleier
- ☐ Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

- ☐ Uten tvil svært ofte
- ☐ Svært ofte
- ☐ Ikke så veldig ofte
- ☐ Ikke i det hele tatt

14. Jeg kan glede meg over en god bok eller et radio eller TV-program

- ☐ Ofte
- ☐ Fra tid til annen
- ☐ Ikke så ofte
- ☐ Svært sjelden

Rikshospitalet – Radiumhospitalet HF

Glutenstudiene 2014

Versjon: Baseline

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 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 deprimert 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 ukene?

☐ Ingen ☐ Moderate

☐ Meget svake ☐ Sterke

☐ Svake ☐ Meget sterke

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

☐ Hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

☐ Endel av tiden

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det den siste 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?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

B. Følt deg veldig nervøs?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

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

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

D. Følt deg rolig og harmonisk?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

E. Hatt mye overskudd?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

F. Følt deg nedenfor og trist?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

G. Følt deg sliten?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

H. Følt deg glad?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

I. Følt deg trett?

☐ Hele tiden ☐ Endel av tiden

☐ Nesten hele tiden ☐ Litt av tiden

☐ Mye av tiden ☐ Ikke i det hele tatt

J. løpet av den siste uken, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

- ☐ 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	☐	☐	☐	☐	☐
B) Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
C) Jeg forventer at min helse vil bli dårligere	☐	☐	☐	☐	☐
D) Min helse er utmerket	☐	☐	☐	☐	☐

Oslo universitetssykehus

Glutenstudiene Versjon: Baseline

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

Deltaker ID____________________

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

Deltaker ID____________________________