

Dietary intervention reduces  
self-reported symptoms in  
patients with Crohn's disease  
in remission

Master thesis

by

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# Dietary intervention reduces self-reported symptoms in patients with Crohn's disease in remission

**Master thesis in Clinical Nutrition**

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A handwritten signature in black ink, appearing to read 'Maren J. Komperød', written in a cursive style.

*Maren J. Komperød*

*May 2012*



## Sammendrag

**Bakgrunn:** Noen pasienter med inaktiv Crohn's sykdom har symptomer som oppblåsthet og avvikende avføring (42-57 %), som tilsvarer symptomer hos pasienter med irritable tarm syndrom (IBS). En pilotstudie fant at en eliminasjonsdiett der fermenterbare karbohydrater (FODMAPs) var begrenset, reduserte symptomer hos slike pasienter. Intervensjoner med endring av matvarevalg, der IBS pasienter har fått symptomlindring, kan muligens overføres til pasienter med inaktiv Crohn's sykdom som opplever IBS lignende symptomer. Videre er det vist at pasienter med inaktiv Crohn's sykdom ofte opplever symptomer som ikke er knyttet til mage- tarm funksjonen, f.eks utmattelse og ledd- og muskelsmerter. Få kostholdsintervensjoner er gjennomført med disse symptomene som utfall. Denne studien hadde som mål å utforske om en kostholdsintervensjon der matvarer som er assosiert med symptomreaksjoner hos IBS pasienter, kunne redusere symptomer hos pasienter med inaktiv Crohn's sykdom som opplevde symptomer knyttet til matinntak.

**Metode og utvalg:** En åpen prospektiv studie ble gjennomført hos pasienter med inaktiv Crohn's sykdom (definert som calprotectin  $< 250 \mu\text{g/g}$  i feces) med selvrapporterte symptomer knyttet til matinntak. Pasientene spiste som vanlig i to uker (baseline), inkludert matvarer med hvete og kumelk. Pasientene fulgte så en to-ukers eliminasjonsdiett etterfulgt av en individuell gradvis reintroduksjon av matvarer i fire til ni uker. Hvis en matvare skapte symptomer, ble den kuttet ut. Alvorlighetsgrad av totale symptomer, magesmerter, oppblåsthet, avvikende avføring, luftavgang, utmattelse og ledd-muskelsmerter ble evaluert ved at pasientene måtte fylle ut en visuell skala, (VAS, 0-10 cm) og en mat- og symptomdagbok. Matvarer rapportert som symptomutløser under reintroduksjonsfasen ble sammenlignet med de matvarene som ble rapportert ved studiestart.

**Hovedresultater:** Totalt 12 pasienter (alder 23-66 år, fire menn) fullførte kostholdsintervensjonen. En symptomreduksjon ble funnet ved alle symptomene ( $P < 0.05$ ) fra baseline til eliminasjonsdietten, men det ble ikke funnet en økning i symptomer fra eliminasjonsperioden til studie-ende punkt ( $P > 0.05$ ). Matvarer som inneholder kumelk og hvete var de matvarene som skapte hyppigst symptomer i denne pasientgruppen.

**Konklusjon:** Kostholdsintervensjoner kan muligens føre til en symptomreduksjon hos pasienter med inaktiv Crohn's sykdom med selvrapporterte symptomer. Det er uvisst hvilke underliggende mekanismer som trigger disse symptomene.





## Abstract

**Objectives:** Patients with Crohn's disease (CD) often (42-57 %) report food hypersensitivities with symptoms like bloating and abnormal feces, similar to symptoms in patients with irritable bowel syndrome (IBS), despite being in remission. One pilot study found that a dietary intervention low in fermentable carbohydrates (FODMAPs) decreased symptoms in CD patients. Dietary interventions carried out on patients with IBS may be transferable to CD patients in remission with self-reported hypersensitivities. Furthermore, patients with CD often experience extraintestinal symptoms like fatigue and musculoskeletal pain, however investigation on the efficacy of dietary interventions on these symptoms are lacking. This study was set out to explore the efficacy of a dietary intervention, based on symptom triggers in IBS, on patients with CD in remission with self-reported food hypersensitivities.

**Methods:** An open prospective study was undertaken in patients with CD in clinical remission (defined as calprotectin < 250 µg/g in feces) with self-reported reactions to food intake. The patients followed their habitual diet including foods with wheat and cow's milk for two weeks. This was followed by a two-week strict elimination diet and a gradual reintroduction of individual food-items for 4 to 9 weeks. If a reaction occurred, the suspected food-item was excluded. Symptom severities of total symptoms, abdominal pain, bloating, abnormal feces, wind, fatigue and musculoskeletal pain were evaluated using a visual analogue scale (VAS, 0-10 cm) and food- and symptom diary. The food symptom triggers identified during the reintroduction period were compared to the self-reported symptoms and the symptom triggers collected at the introduction meeting.

**Main results:** A total of 12 patients (aged 23-66 years, four men) completed the intervention. Whereas all symptoms decreased ( $P < 0.05$ ) from baseline to the elimination period, they did not increase ( $P > 0.05$ ) from the elimination period to the last week of the reintroduction period (endpoint). The most frequent symptom triggers were cow's milk products and wheat products.

**Conclusion:** Dietary interventions may reduce self-reported symptoms in patients with CD in remission. Still, the underlying mechanism causing the food hypersensitivity reported by the CD patients in this study remains unknown.



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## Abbreviations

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<b>CD</b>	Crohn's Disease
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<b>FODMAPs</b>	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
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<b>FOS</b>	Fructo-oligosaccharides
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<b>GI</b>	Gastrointestinal
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<b>GOS</b>	Galacto-oligosaccharides
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<b>HRQoL</b>	Health-related Quality of Life
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<b>IBD</b>	Inflammatory Bowel Disease
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<b>IBS</b>	Irritable Bowel Syndrome
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<b>IgE</b>	Immunoglobulin E
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<b>LMF</b>	Landsforeningen mot fordøyelsessykdommer (Norwegian Association of Digestive Disorders)
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<b>MSG</b>	Monosodium Glutamate
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<b>VAS</b>	Visual Analogue Scale
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## Preface

Dr. Arne Røseth, a gastroenterologist at Lovisenberg Diakonale Hospital, Oslo, suggested the idea behind this master thesis. He had experienced patients with Crohn's disease complaining about adverse reactions to food intake even if they had mucosal healing and normalized calprotectin levels in feces. He discussed his thoughts with immunologists, who implicated that disease activity and ulcers in the intestines can dispose for later progression of food allergy, due to a 'leaky gut.' During the same time period, the low-FODMAP diet, developed by colleagues at the Monash University in Australia, captured Dr. Røseth's interest as their approach had impressive results in patients with irritable bowel syndrome. Dr. Røseth and clinical dietitian Tonje Mellin-Olsen later contacted the University of Oslo to discuss the opportunity for a master thesis and this is the result.



# 1 Introduction

Self-reported gastrointestinal (GI) symptoms are common and 35 % of the Western general population reportedly have food allergy [7]. However, when using the 'gold standard' double-blind placebo-controlled food challenge to verify adverse reactions to food-items, the prevalence is only 1-2 % [8, 9]. There is a gap between medically diagnosed and self-reported reactions to food-items [10]. The underlying causes of self-reported symptoms to food-items often remain unknown. GI symptoms that cannot be explained by disease are often diagnosed as functional bowel disorders [11]. A common functional bowel disorder is called the irritable bowel syndrome (IBS). For some patients, IBS is the consequence of intestinal inflammation caused by bacteria (food poisoning) [12, 13].

CD is a chronic inflammatory bowel disease. Patients with CD in remission often report symptoms similar to those with IBS [14-16]. Importantly, symptoms like those in IBS may affect health-related quality of life [15, 17]. Dietary advice related to food hypersensitivity symptoms in patients with CD are limited. However, dietary interventions aimed to reduce symptoms in patients with IBS have been investigated thoroughly. Recent research has highlighted intestinal luminal distension caused by some carbohydrates as an important mediator of symptoms in IBS [3, 18]. Identification of food-items that may lead to luminal distension is the basis of a new dietary intervention called the FODMAP approach.

FODMAPs refers to highly fermentable carbohydrates, and are common in the Western diet [3]. Interestingly, a pilot-study [19] indicated that a diet low in FODMAPs may also reduce symptoms in patients with CD in remission. Hence, dietary approaches investigated on IBS patients may be transferable to patients with CD in remission experiencing the same symptoms.

Furthermore, extraintestinal symptoms [20] such as fatigue [19, 21] and musculoskeletal pain [20] are also common symptoms in patients with CD, even if the disease is in remission. However, few studies have explored the efficacy of a dietary alteration with fatigue and musculoskeletal pain as outcomes. Presently, to our knowledge, studies on dietary interventions to reduce symptoms for CD patients in remission are scarce.

## 1.1 Terminology

There are several terms used to describe adverse GI symptoms related to food intake, e.g. functional gut symptoms, IBS-like symptoms, food intolerance and food hypersensitivity. Self-reported food hypersensitivity is a neutral term and does not indicate a mechanism for the adverse reactions, and this term will be used further to describe self-reported, adverse symptoms related to food intake. Furthermore, extraintestinal symptoms are often related to inflammatory manifestations in CD affecting other organs than the intestines. In the present study, this term is used to describe self-reported fatigue and musculoskeletal pain.

## 2 Crohn`s Disease

Inflammatory bowel disease (IBD) refers mainly to ulcerative colitis and Crohn`s disease (CD). The latter is a chronic relapsing inflammatory disease [5]. CD can affect any site of the gastrointestinal (GI) tract (fig. 1), from mouth to rectum, in contrast to ulcerative colitis, which affects only the colon. The inflammation in CD often has a patchy pattern [5]. The small intestine is affected in 30 %, colon in 40 % and both small intestine and colon in approximately in 30 % of CD patients [22]. In Norway, around 200-300 are diagnosed with CD each year and the onset is most common around 15-25 years of age [5]. Interestingly, it seems like the incidence of CD in Norway is increasing [23].

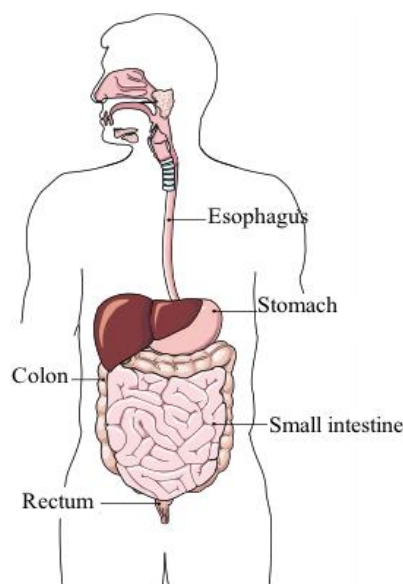


Figure 1. The gastrointestinal tract. Figure from the Norwegian Association of Digestive Disorders` leaflet [5], modified by the author

### 2.1 Aetiology

The aetiology of CD is not completely understood. Genetics, environment and the gut flora (microbiota) all play a role [24]. Smoking [25] is known as a major risk factor for developing CD. In addition, having a first degree relative with CD [26, 27] increases the risk of developing CD by 10-fold and strongly implies a genetic involvement [27]. In addition, research has identified several genes associated with CD [28]. The `hygiene hypothesis` proposes that increased focus on hygiene in the Westernized part of the world may contribute

to the increased prevalence of autoimmune diseases [29, 30]. Furthermore, it has been proposed that a 'Westernized diet' promotes susceptibility to CD, especially due to the increased intake of sugar and fats (common ingredients in 'fast food') [31-33]. However, there is still no significant evidence that dietary intake can trigger the disease [31].

## 2.2 Gut Microbiota

The GI tract comprises a large colonization of bacteria (microbiota) situated in the colon and the distal small intestine [34]. The microbiota can vary between individuals, dietary habits and health of the host [35]. This colonization is essential for processing nutrients, development and maintenance of the epithelial barrier, immune function and resistance to colonization of foreign pathogens [35]. On the other hand, alterations of the microbiota can possibly contribute to the onset of disease [35]. Dietary changes in developed countries through the last four decades have been linked to changes in the microbiota and the increased incidence of inflammatory diseases [30]. Moreover, the increased focus on hygiene may possibly lead to less exposure to some critical bacteria which affect the intestinal microbiota and hence the immune regulation [31]. Depletion of some beneficial bacteria has been associated with CD [35]. Still, more research is needed to find whether the changes in microbiota are the cause or effect of inflammation in humans [35].

### 2.2.1 Alteration of the Microbiota in Crohn's Disease

An altered microbiota in predisposed individuals has been implied as one possible aetiology of CD [36]. Hence, the use of antibiotics, probiotics and prebiotics has been proposed for restoration of the potentially dysregulated microbiota [36]. The rationale for the use of antibiotics is that it could possibly eradicate pathogenic bacteria. Antibiotics have been suggested as a supplementary therapy to prevent relapse of CD, however the optimal antibiotic regimens in different CD patients remain uncertain [36]. Probiotics have been defined as '*living microorganisms which upon ingestion in certain numbers exert health benefits beyond inherent general nutrition*' [37]. Probiotics are found in foods such as yoghurt or as supplements. The supplementation or intake of probiotics could in theory enhance the number of beneficial bacteria in the gut [36]. Furthermore, prebiotics refers to malabsorbed carbohydrates and fibers that are fermented by the microbiota in the colon. Short chain fatty acids are byproducts of this fermentation [38]. These fatty acids are energy



substrates for the intestinal epithelial cells and are important in the maintenance of the intestinal barrier function and in the regulation of immune responses [30]. Hence, intake of pro- and prebiotics may affect the homeostasis of the microbiota.

### 2.2.2 Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth denotes an abnormal expansion of the microbiota in the small intestine [39]. The gut bacteria move into the small intestine to access ingested carbohydrates and this can lead to changes in the site of fermentation [34]. One study found that small intestinal bacterial overgrowth might lead to abnormal hydrogen breath tests and possibly lead to a false diagnosis of carbohydrate malabsorption. This was indicated as the hydrogen breath tests normalized when small intestinal bacterial overgrowth was eradicated by antibiotics [34]. Another study found that 20 % of the patients with CD had small intestinal bacterial overgrowth [40]. Small intestinal bacterial overgrowth has also been found in patients with IBS (23-75 %) [34, 39, 41]. Symptoms like bloating and diarrhea has been indicated as predictors of small intestinal bacterial overgrowth in IBS patients [41]. In CD, small intestinal bacterial overgrowth was associated with symptoms like bloating, abdominal pain and diarrhea [40].

## 2.3 Diagnosis and Treatment

CD is diagnosed by endoscopic investigation and biopsies of the colon and proximal small intestine [5]. Medical treatment aims to heal intestinal mucosa, normalize the patients' health-related quality of life (HRQoL) and minimize and prevent hospitalization. Additionally, it should confer acceptable side effects for the patient [5]. Corticosteroids have been the main medical drug treatment for patients with CD, but is today often replaced by tumor necrosis factor  $\alpha$  inhibitors [5].

### 2.3.1 Calprotectin

Calprotectin is a protein found in macrophages and neutrophil granulocytes [42]. Calprotectin is involved in inflammatory reactions and is increased in an acute inflammatory phase [43]. In CD, calprotectin level in feces is used as an inflammatory marker and has been suggested as the best marker of intestinal inflammation available today [42]. A calprotectin level less than 250  $\mu\text{g}$  per g of feces has been indicated to reflect mucosal healing in patients with CD [42].

## 2.4 Health Related Quality of Life

CD can impact a patient's HRQoL, and is often influenced by disease activity but may also be altered when disease is in remission [44]. Patients with CD often report pain caused by mental stress or caused by food intake [45]. Pain may be present despite remission of the disease and this may affect HRQoL [45]. A study found that unemployment and sick leave were more common in Norwegian patients with CD than in the general Norwegian population and this affected the HRQoL [46]. HRQoL may also be altered by adverse symptoms related to food intake in patients with CD [16, 47].

## 2.5 Clinical Features

Patients with CD often experience adverse symptoms [48]. These symptoms may vary depending on the extent of the disease [1]. Symptoms such as diarrhea, sudden urge to go to the toilet, abdominal pain, abdominal cramps, fever, nausea and vomiting are prominent [22, 48]. The inflammation in CD can consequently lead to formation of fistula<sup>1</sup>, abdominal abscesses, and obstruction of the affected or previously affected intestinal site [22]. Due to this, nutritional status is often altered.

## 2.6 Nutritional Challenges

The clinical features of CD may cause some nutritional challenges. For example, in some CD patients the dietary protein requirements may be increased [49]. Follow-up of nutritional status is especially important in children with CD to prevent growth failure [49].

Inflammation may cause malabsorption and lead to nutritional deficiencies [1]. Hence, patients may benefit from individual dietary advice and sometimes nutritional supplementation, depending on where the disease is situated [50]. In addition, extensive inflammation can affect appetite and lead to a poor dietary intake [1]. Chronic diarrhea can result in loss of nutrients e.g. magnesium, calcium, zinc, and loss of electrolytes e.g. sodium and potassium [1]. Furthermore, a poor dietary intake and the use of corticosteroids can lead to osteoporosis [1]. Intake of fibrous foods may lead to mechanical obstruction caused by intestinal strictures (narrowing of lumen) [51]. Adverse symptoms related to food intake are

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<sup>1</sup> Fistula refers to an abnormal passageway to e.g. other sites of the bowel, the urinary bladder, perianal or vagina.

also common in patients with CD and may cause restriction of dietary intake [51]. An overview of some nutritional challenges in CD and potential causes are stated in table 1.

Table 1. Potential causes of nutritional challenges in CD [1]

<b>Nutritional challenge</b>	<b>Potential causes</b>
Weight loss, increased energy and nutrient requirements	Inflammation leading to malabsorption, poor appetite, surgery
Malabsorption	Fructose- or lactose malabsorption, surgery, bile salt malabsorption, inflammation
Poor dietary intake	Abdominal symptoms, exclusion of food symptom triggers, decreased appetite, nausea and/or vomiting caused by strictures or stenosis
Increased intestinal losses	Inflammation, diarrhea, malabsorption, vomiting
Anaemia	Poor dietary intake, blood loss
Nutrient deficiencies (e.g. folate, vitamin B <sub>12</sub> , magnesium, zinc, electrolytes, calcium, vitamin D)	Diarrhea, malabsorption, disease activity in stomach or ileum (vitamin B <sub>12</sub> deficiency), vomiting, short-bowel syndrome*

\*Short bowel syndrome refers to the consequences of surgical removal of the intestines [52]

## 2.7 Dietary Guidelines for Patients with Crohn's Disease

Practical guidelines have been developed by several interest organizations such as The American Dietetic Association [53]. The guidelines generally consist of recommended foods and foods to avoid. However, no specific dietary interventions are mentioned. The American Dietetic Association general guidelines for both ulcerative colitis and CD are as follows; meals every third or fourth hour, try foods that are low in fiber, drink enough fluids, eat foods with pro-and prebiotics, take multivitamins and try to introduce whole grains in periods with no symptoms [53]. The Norwegian Association of Digestive Disorders (Landsforeningen mot fordøyelsessykdommer) also provides limited dietary advice for this patient group. In one of their information brochures [50], they advice patients with strictures in the intestinal lumen to

avoid fiber-rich foods that may cause obstruction. They furthermore inform that diet has no considerable impact on progression of CD itself, but mention that cow's milk may cause diarrhea. In addition, they inform that patients with intestinal resections or poor nutritional status may need follow-up from a clinical nutritionist [50]. Notably, advices from clinical nutritionists were not found in these brochures.

## 2.8 Dietary Therapy to Prevent Relapse of Crohn's Disease

Some studies have suggested that diet may prevent relapse in CD patients in remission. One study concluded that a semi-vegetarian diet was effective in preventing relapse in patients with CD in remission [54]. The semi-vegetarian diet used in the study was based on a Japanese diet with brown rice instead of white rice and foods high in fiber. The aim was to introduce a diet that would increase beneficial bacteria in the gut by eating foods high in prebiotics. The diet consisted of fruit, vegetables, legumes, eggs, milk, miso (Japanese seasoning), potatoes, plain yoghurt and 1/2 serving of fish every week and 1/2 serving of meat every two weeks. Sweets, bread, cheese, butter, margarine, juice and 'fast foods' were avoided. Sixteen patients followed the diet with a compliance rate of 73 %. After one year 100% of the patients in the semi-vegetarian diet group were still in remission and 92 % after two years. Furthermore, Jones *et al.* (1985) investigated the relapse rate of 20 CD patients in remission. Remission was induced by an elemental diet or total parenteral nutrition. One group was put on an unrefined, fiber rich carbohydrate diet. The other group followed an elimination diet based on eliminating foods they were intolerant to, most frequently wheat- and dairy products. In the latter group, 7 of 10 remained in remission after six months compared to none in the unrefined carbohydrate group [55]. However, the sample sizes in these two studies were rather small and the inflammation rate could be affected by other factors.

Furthermore, due to the anti-inflammatory properties of omega-3 fatty acids, supplements of these fatty acids has been suggested to prevent relapses of CD [49]. However, two randomized controlled trials on 753 CD patients in remission found no significant difference in relapse rate between the placebo group and the group taking supplementation of omega-3 free fatty acids (4g/ day) [56]. The evidence available today suggest that enteral nutrition (liquid feeds) may prevent relapses in CD patients, as supplementary to normal foods, or as an alternative to drug therapy [57]. However, larger studies are requested to confirm this.

## 2.9 Extraintestinal Manifestations in Crohn's Disease

CD mainly affects the GI tract, however the inflammation can also affect other organs [22, 58]. These are called extraintestinal manifestations and are often presented as musculoskeletal or skin manifestations [20]. Extraintestinal symptoms seems to be more prevalent in CD patients than in patients with ulcerative colitis [58].

### 2.9.1 Musculoskeletal Pain

It is indicated that approximately 10 % of the general population report chronic musculoskeletal pain, with higher rates among females [59]. Musculoskeletal manifestations are described as all clinical features of spondylarthropathies, which constitutes a group of conditions characterized by inflammation of the joints [60]. Furthermore, one study found that 22 % of patients with CD had joint pain not related to inflammation [61], and this was associated with a decreased HRQoL [61]. There seems to be a lack of research on the possible efficacy of dietary interventions on self-reported musculoskeletal symptoms.

### 2.9.2 Fatigue

Fatigue has been described as '*a persistent, over-whelming sense of tiredness, weakness or exhaustion resulting in a decreased capacity for physical and/ or mental work*' [21]. Fatigue is a diffuse symptom, and has been found to be more prevalent in patients with CD in remission than in healthy controls [62]. Fatigue is also associated with a decreased HRQoL [62]. One study found that 22 % of the CD patients had chronic fatigue (fatigue more than six months) [63]. Furthermore, there are limited studies on the efficacy of dietary interventions on patients with CD in remission with fatigue as an outcome. Interestingly, a study comparing IBS-patients when ingesting a high and low FODMAP diet found that IBS-patients reported significantly more fatigue on the high FODMAP diet, and no change was found in the healthy controls [64]. This may be transferable to CD patient with symptoms similar to IBS.

### 3 Possible Mechanisms Behind Adverse Reactions related to Food Intake

The following sections include descriptions of functional bowel disorders, IBS, allergic hypersensitivity, non-celiac gluten intolerance, bioactive chemicals and adverse reactions to foods caused by luminal distension (FODMAPs). These are possible mechanisms or conditions that may cause adverse reactions to food intake. Self-reported hypersensitivities are often diagnosed as IBS if no organic disease can be found [11]. However, it has been proposed that there may be other conditions underlying the IBS that are with today's diagnostic tool difficult to detect [65].

#### 3.1 Food Hypersensitivity

In 1995 the European Academy of Allergy and Clinical Immunology published a paper aimed to create a consensus of adverse food reactions terminology. In 2001 the position paper was revised and proposed that 'hypersensitivity' should be used as an umbrella term for all abnormal reactions to skin and mucosa. The definition was as follows: *'Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects'* [6]. As seen in figure 2, hypersensitivity can be divided into allergic hypersensitivity (immunologic reaction detected or strongly suspected) and non-allergic sensitivity (immunologic reaction excluded) [6]. Notably, several causes of hypersensitivity symptoms may be present in a patient at the same time [6].

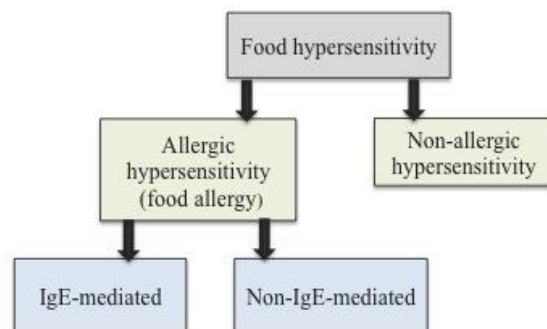


Figure 2. Food hypersensitivity definitions, by European Academy of Allergy and Clinical Immunology [6]. Illustration made by the author

### 3.1.1 Allergic Hypersensitivity

Allergy or allergic hypersensitivity, was by the European Academy of Allergy and Clinical Immunology defined as *'a hypersensitivity reaction initiated by immunologic mechanisms'* [6]. The most common antibodies to cause reactions are immunoglobulin-E (IgE) isotypes [6]. Allergic hypersensitivity can be divided into IgE-mediated reactions, non-IgE-mediated reactions or mixed IgE and non-IgE-mediated reactions. Common allergic diseases are asthma, rhinitis and skin diseases such as eczema/dermatitis [6]. The US Food and Drug Administration [66] identified proteins from cow's milk, eggs, tree nuts, peanuts, shellfish, fish, wheat and soy as the eight most common allergens, which account for 90 % of allergic reactions to food-items.

#### *Allergic Hypersensitivity in Crohn's Disease*

There may be a link between CD and allergic hypersensitivity. The inflammation in CD may theoretically damage the intestinal barrier, possibly lead to a 'leaky gut' and dispose this patient group to develop allergic hypersensitivity. A 'leaky gut' refers to increased permeability and impaired barrier function of the intestines. Increased intestinal permeability has been associated with IgE-mediated allergic hypersensitivity [67, 68] and also with non-IgE mediated reactions to food-items [68]. Furthermore, the intestinal barrier function may be altered in CD patients [69, 70] and also in their first-degree relatives [71, 72]. The theory states that due to increased permeability of the intestines, molecules (e.g. antigens from food) may penetrate the mucosa, passage into the bloodstream and trigger the immune system [69, 73]. Still, it is uncertain if the increased permeability is the cause or the consequence of the altered immune activation.

## 3.2 Functional Bowel disorders

IBS refers to a functional bowel disorder with features of GI symptoms [74]. IBS is a diagnosis often given to patients with GI symptoms where other diseases are excluded [11]. IBS has been defined as a *'group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation'* [75]. The worldwide prevalence is estimated to be 10-15 % [76]. IBS has also been associated with symptoms like dizziness, fatigue and muscle pain [77]. It

seems like IBS is the functional bowel disorder that is most commonly referred to and investigated in the literature of functional bowel disorders and food intolerances.

As presented in figure 3, functional bowel disorders also include functional constipation, functional diarrhoea, functional bloating, unspecified functional bowel disorder in addition to IBS [74]. Bloating, abdominal pain and abnormal bowel habits are among other GI symptoms referred to as 'functional gut symptoms'. Foods are often described as symptom triggers by patients experiencing these symptoms [65]. It has been suggested that the underlying mechanism should be identified before a dietary approach is chosen, however, this may be difficult with today's diagnostic tools [65]. There may be other underlying mechanisms of the symptoms diagnosed as functional bowel disorders and IBS such as bioactive chemicals and luminal distension [65]. The past two will be discussed further. In addition, there are some indications that functional gut symptoms may be caused by allergic food hypersensitivity [11]. Still, improved methods to identify food-items that trigger the immune system and more reliable biomarkers to identify individuals with allergic food hypersensitivity are requested [65].

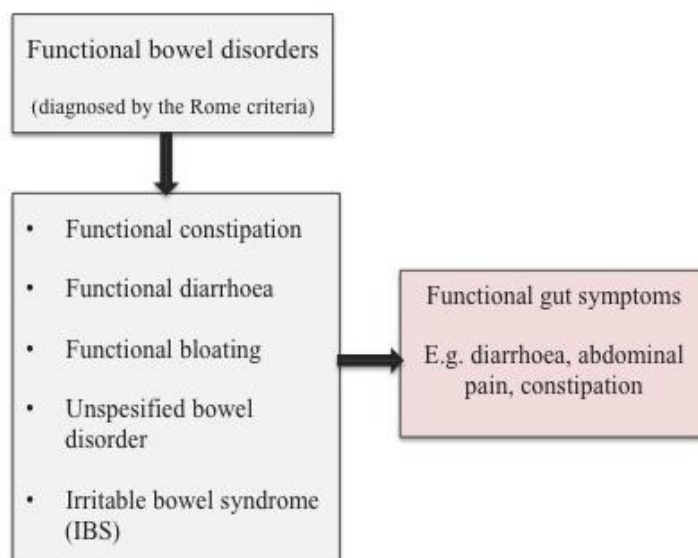


Figure 3. Functional bowel disorders. Illustration made by the author



### 3.2.1 The Rome Criteria

Functional bowel disorders and the IBS are diagnosed by the Rome criteria [2, 74]. The last updated version (Rome criteria III) was published in 2006. The diagnostic criteria for IBS are stated in table 2.

Table 2. The Rome III criteria for diagnosis of IBS [2]

Recurrent abdominal pain or discomfort at least 3 days during one month in the last 3 months associated with two or more of the following:		
1. Onset associated with a change in form (appearance) of stool	2. Improvement with defecation	3. Onset associated with a change in frequency of stool

### 3.2.2 Post-infectious Irritable Bowel Syndrome

Post-infectious irritable bowel syndrome (post-infectious IBS) often occurs after an incident of acute food poisoning called bacterial gastroenteritis [12, 13, 78, 79]. However, there are still many uncertainties about the onset of post-infectious IBS. Subclinical inflammation and changes in the microbiota and barrier function of the gut are possible contributors [79]. A study found that of the 75 patients admitted to a hospital with acute gastroenteritis, 20 patients had symptoms similar to post-infectious IBS after six months [12]. Another study investigated the prevalence of GI symptoms in 544 patients previously admitted to a hospital with bacterial gastroenteritis. They found that 25 % developed altered bowel habits and 7 % developed post-infectious IBS [13]. Additional risk factors associated with development of post-infectious IBS, were duration and type of infection, smoking and stressful life events [80]. This implies that inflammation may play a part in the development of IBS in some patients.

### 3.2.3 Irritable Bowel Syndrome and Allergic Hypersensitivity

There may be some associations between IBS and allergic hypersensitivity. One study found that IBS was more common in patients with allergic symptoms such as asthma, rashes, itchy eyes and swelling of mouth [11]. Another study found that patients who reported food hypersensitivities, 93 % had IBS and 61 % had allergic hypersensitivity [81]. There seems to

be an association between allergic hypersensitivity and IBS. Still, it is unknown if this represents a direct clear link or if patients with IBS report more symptoms or has better knowledge about food hypersensitivity than the general population [81].

### 3.2.4 Symptoms Similar to Irritable Bowel Syndrome in Crohn's Disease

Studies have investigated the prevalence of IBS-like symptoms in patients with CD in remission [15, 16, 82]. In studies where the IBS-like symptoms were identified by the Rome criteria, the prevalence was 42-45 % [15, 16]. In another study a questionnaire (Gastrointestinal Symptom Rating Scale) was used to identify IBS-like symptoms, and the prevalence was found to be 57 % [82]. The mechanisms behind these symptoms in CD are uncertain. Psychological factors [82] have been suggested as a possible contributor. In addition, preceding inflammation leading to an 'irritable bowel' in CD patients has also been suggested [15]. Furthermore, small intestinal bacterial overgrowth has been found in both IBS and CD patients, suggesting that this may also contribute to adverse symptoms in some patients.

## 3.3 Bioactive Chemicals

The bioactive chemicals salicylates, amines and glutamates have been reported to cause adverse symptoms in some individuals [65]. Salicylates are found in e.g. alcohol beverages, herbs, fruits and vegetables [83], but also in some drugs and food preservatives [84]. Salicylate intolerance has been suggested to cause abdominal pain, diarrhea, swelling and asthma [84]. Monosodium glutamate (MSG or E-621) is a flavor enhancer and has been associated with the induction of migraine headache and asthma [85]. However, there seem to be no consistent data to support this [85]. Amines such as histamines are found in fermented foods such as matured cheese and in wine. Foods rich in histamines, or foods that provoke histamine release e.g. citrus fruits, may cause diarrhea, flushing, headache and asthma [86]. However, well-designed studies on the reactions to food chemicals are needed, as these reactions may be difficult to detect. Exclusion of these food-items may also lead to a less palatable diet and hence have nutritional consequences [65].

### 3.4 Luminal Distension and the FODMAP approach

A relatively new approach to reduce adverse symptoms in IBS patients has been developed at Monash University, Australia by Shepherd *et al.* [3]. This approach is based on the ingested foods' effect on the intestinal lumen and that some individuals may be more sensitive to these effects. Importantly, patients experiencing adverse symptoms to FODMAPs do not necessarily consume more of these foods than others without symptoms. However, some may be more sensitive to the mechanisms [3]. Some food groups have properties that can result in luminal distension. These components are given the acronym 'FODMAPs' (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols). FODMAPs include oligosaccharides (fructans and galactans), disaccharides (lactose), monosaccharides (fructose) and polyols such as sorbitol, xylitol, maltitol and mannitol [3]. Dietary FODMAPs have some common functional characteristics that can occur in all individuals.

As demonstrated in figure 4, FODMAPs may be malabsorbed poorly or not at all in the small intestine. In addition, FODMAPs are small molecules and can create an osmotic effect, which can increase water delivery to the colon [3]. Furthermore, when colonic bacteria ferment malabsorbed FODMAPs, gas is produced. These mechanisms can cause GI symptoms, such as osmotic diarrhea, bloating, wind and abdominal pain in susceptible patients.

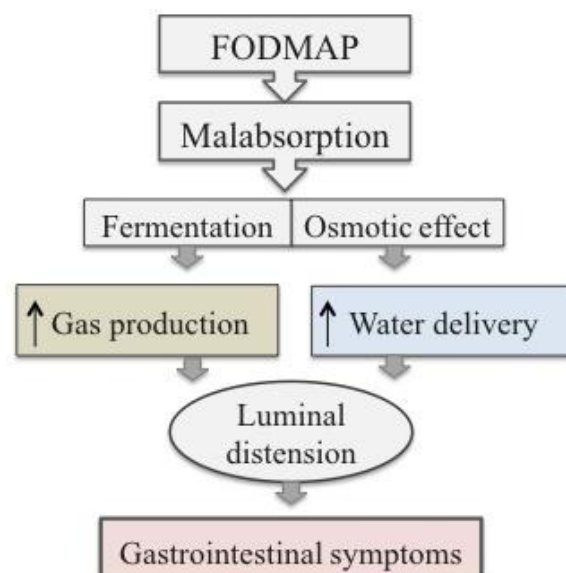


Figure 4. FODMAP intake and proposed mechanisms inducing GI symptoms. Illustration made by the author

### 3.4.1 Visceral Hypersensitivity

Some individuals may be more sensitive to the intestinal distension caused by liquids or gas [87], causing abdominal pain [88]. This is called visceral hypersensitivity. In IBS patients a lower threshold of pain has been indicated [89]. This was demonstrated in a study where a balloon was inflated in the sigmoid colon. They found that patients diagnosed with an irritable colon experienced more pain to the distension of the sigmoid colon than the healthy controls [90]. The mechanisms leading to visceral hypersensitivity in IBS patients are uncertain, but increased sensitization after an inflammation such as by gastroenteritis or increased intestinal permeability have been suggested [89]. It can be proposed that this visceral hypersensitivity may be present in CD patients as well, due to preceding inflammation.

### 3.4.2 Gut Motility

FODMAPs may increase the liquid and gas contents of the bowel and distend the intestinal lumen. This may alter gut motility [18]. Distension of the intestinal lumen may lead to disturbed gut motility as was shown by Clausen *et al.*. They showed that lactulose, a synthetic FODMAP that is malabsorbed and has a high osmotic effect, increased the liquid contents in the small bowel lumen and caused diarrhea [91].

### 3.4.3 Fermentation

Malabsorbed FODMAPs are quickly fermented by bacteria [3]. Gases like hydrogen, carbon dioxide and in some individuals methane are produced. In normality, the gases are absorbed and released by the respiratory system to prevent distension and adverse symptoms [87, 88]. However, the production of gas may be so rapid that it increases the lumen and produces excessive wind [87]. In some individuals the mechanisms of gas evacuation may be insufficient, initiating distension of the lumen [88]. The migration of bacteria into the small intestine when small intestinal bacterial overgrowth is present, may cause increased fermentation and gas production in the small intestine [34]. Distension of the small intestine has been shown to produce more pain than distension of the colon [92]. A study investigated hydrogen and methane breath tests and symptoms in 15 IBS-patients and 15 healthy subjects following a high and low FODMAP diet [64]. The healthy subjects reported increased wind on the high FODMAP diet. In comparison, the IBS-group reported a significant increase of all GI symptoms and fatigue on the high FODMAP diet. This may confirm the theory that some individuals are more sensitive to luminal distension. Furthermore, the study also found that

the low FODMAP diet reduced the amount of hydrogen gas produced in both groups. However, the IBS-group produced more hydrogen gas in general than the healthy subjects [64]. This suggests that there may be some differences gas production by the microbiota in IBS patients compared to the healthy subjects in this study.

In sum, reduction of FODMAPs is proposed as an efficient dietary intervention for reducing symptoms in individuals with IBS. Notably, this has also been indicated in patients with CD in remission [19]. The five main food components of the FODMAP approach are discussed further.

### 3.4.4 FODMAP sources

FODMAPs are found in many foods commonly used today. Table 3 provides an overview of some common FODMAP sources and their absorption capacity in the small intestine.

Table 3. Common sources of FODMAPs in the diet and absorption capacity in the small intestines. Modified table from Gibson & Shepard [3]

Food component	Dietary form	Example of sources	Absorption capacity
Fructose	Fructose	Fruits, honey, high fructose corn syrup	Malabsorption is present in all humans when the load of free fructose is sufficiently large  Some individuals have limited absorption capacity. Prevalence of this fructose malabsorption vary from 30-80 % [93] in the general population
Lactose	Lactose	Milk, yoghurt, ice cream	Approximately 70 % of the worldwide population [51] and 3 % of the Scandinavian population [94] lack the enzyme lactase  No absorption if lactase deficient
Fructans	Fructo-oligosaccharide	Wheat, onions	Humans lack the enzymes for hydrolyzation in the small intestine
Polyols (sugar alcohols)	Sorbitol, xyitol, mannitol, maltitol	Apples, pears, plums, artificial sweeteners	Poorly absorbed in the small intestine, passive absorption < 20 %
Galacto-oligosaccharides	Raffinose, stachyose	Legumes, beans, cabbage, brussel sprouts, onions	Humans lack the enzyme, $\alpha$ -galactosidase, for hydrolyzation. Minimal absorption
Other	Polydextrose, isomalt	Reduced caloric sweetener	Poorly absorbed in the small intestine, passive absorption < 20 %

### *Fructose*

Fructose is one of the components of the disaccharide sucrose, and can be found in polymerized form as fructans [87]. Fructose is often used as a sweetener and as high fructose corn syrup. When ingestion of fructose exceeds the absorption capacity of the gut, GI symptoms may occur [65]. However, malabsorption of fructose is not present in all individuals. Absorption capacity is dependent on the amount of glucose consumed at the same time as fructose and transit time [65]. Importantly, fructose is only a FODMAP when it is malabsorbed. In a study comparing the prevalence of fructose malabsorption among healthy subjects compared to subjects with intestinal disorders, fructose malabsorption was found to be more frequent in CD (61 %) than the other patient groups. The reason for this is uncertain, however loss of absorptive surface has been suggested [95]. Notably, the hereditary metabolic fructose intolerance disorder is not covered in this thesis.

### *Lactose*

Lactose is a disaccharide found in mammalian milk. Lactose requires the enzyme lactase-phlorizin hydrolase known as lactase, mainly situated in the proximal jejunum, for hydrolysis of lactose to glucose and galactose in the intestine [51]. Glucose and galactose are then absorbed into the bloodstream by intestinal enterocytes for energy utilization. Lactase deficiency results in malabsorption of lactose [51]. The deficiency of lactase can have three different etiologies: congenital, primary or secondary. Congenital deficiency is a permanent and rare disorder present from birth, often characterized by diarrhea when the infant is given mother's milk for the first time [51]. Primary deficiency occurs in approximately 70 % of human beings. However, in Norway the prevalence is only 2-3 % [96] possibly due to the early introduction of dairy farming in the Scandinavian area [51]. The mechanism behind secondary deficiency is the loss of lactase due to GI disease, for example when CD affects the proximal jejunum [51]. Nonetheless, the mechanism is the same: non-hydrolyzed lactose travels down to the colon, fermentation and production of gas result in symptoms like pain, bloating and diarrhea. Lactose is only a FODMAP when lactase deficiency is present.

### *Galactans (Galacto-oligosaccharides or GOS)*

Galactans are found in foods like legumes, beans, onions and brussel sprouts as the oligosaccharides raffinose and stachyose. All humans lack the enzyme  $\alpha$ -galactosidase which hydrolyses these forms into simple sugars available for absorption [97]. Galactans are therefore malabsorbed in all humans. Undigested galactans are delivered to the colon for fermentation by the microbiota and gas is produced [98]. Vegetarians often have a high intake of legumes and beans as they are important protein sources in a diet without meat [3].

### *Polyols*

Polyols are found naturally in fruits and vegetables such as apples, pears, cauliflower and mushrooms. Still, polyols are mainly known as artificial sweeteners. They are identified by E-numbers; sorbitol (E420), mannitol (E421), isomalt (E953), maltitol (E965) and xylitol (E967). Artificial sweeteners in e.g. sugar free pastilles or chewing gums are known for their laxative effects [3]. The absorption of polyols varies among individuals and the different types of polyols [65].

### *Fructans*

Fructans are fructose polymers and are called inulins or levans, depending on the number of fructose-fructose bonds [3]. In foods, inulins are the most common fructans. Inulins with chain length less than 10 fructose molecules are called fructo-oligosaccharides (FOS). Inulins with chain length more than 10 fructose molecules are called inulins. The most common forms of inulins found in foods are the FOS [87]. Major dietary sources are onions, garlic and wheat [3].

#### 3.4.5 The Low FODMAP Diet in Practice

Shepherd and Gibson [3] have provided some guidelines for the implementation of the low FODMAP diet. They suggest that before starting a dietary intervention, hydrogen breath tests should be carried out if available, to identify lactose-or fructose malabsorption. This is useful to find if dietary restrictions of these carbohydrates are necessary [3]. Shepard and Gibson further described the instructions given to the patients following the low FODMAP diet. During the elimination period, the patients are advised to avoid foods that contain excess fructose (more fructose than glucose), choose foods where glucose and fructose are in balance and avoid big loads of fructose in one meal, unless fructose malabsorption has been excluded. Furthermore, the patients are advised to restrict lactose if lactose malabsorption is present, to



avoid foods with a high content of fructans and galactans, and to avoid foods high in polyols. The patients are also given information about the FODMAP mechanisms, food lists, meal alternatives and advice for eating away from home. Furthermore, Gibson and Shepherd proposed that a strict low FODMAP elimination diet should be carried out for six-eight weeks. They describe that foods are reintroduced based on tolerance levels and the patient's experience and implies that caffeine-intake, meal size and eating habits should also be considered [3].

#### 3.4.6 Implications of the Low FODMAP Diet

The reduction of FODMAPs may have some disadvantages that should be recognized. Maldigested carbohydrates such as FODMAPs are prebiotics which may have beneficial properties for the microbiota [99]. Restriction of prebiotics could potentially lead to an increase of proinflammatory bacteria and also cause constipation [19]. In addition, the low FODMAP diet may challenge the intake of fiber, as major fiber-sources like wheat are often excluded [3]. A high fiber-intake has been associated with a lower risk of colorectal cancer [100]. The reduction of fruit and vegetables may also be unfortunate as they are important nutrient sources. Additionally, beans and lentils are often the main staple foods in vegetarians and exclusion may challenge the adequacy of their diet. On one hand, restriction of FODMAPs may reduce symptoms and improve HRQoL. On the other hand, ingestion of FODMAPs may be beneficial for the microbiota and the immune system [101]. Further investigations on the long-term effect of FODMAP reduction in relation to these matters are needed.

#### 3.4.7 The FODMAP Approach and Crohn's Disease

A pilot study conducted by Gearry *et al.* [19] investigated the efficacy of a low FODMAP diet in 52 CD patients in remission. Patients received dietary advice based on the low FODMAP diet in a one-to-one session with a clinical nutritionist. The patients also received food lists and written information about the diet and were offered to buy specialized cookbooks. At study initiation it was found that abdominal pain, bloating, fatigue and wind were the most common symptoms. After the intervention a significant improvement in overall symptoms, diarrhea, bloating and wind were found. In overall symptoms, 56 % of the patients reported an improvement after reducing FODMAP intake [19]. However, the results were based on a

structured telephone interview and hence the results should be considered critically. Indeed, the authors [19] requested controlled dietary intervention studies on this group.

### 3.5 Non-celiac Gluten Intolerance

The number of people excluding gluten from their diet, even in the absence of celiac disease seems to be increasing and accordingly the market for gluten-free foods is on the rise. In the US, approximately 6 % are suggested to have what is called non-celiac gluten intolerance [102]. Moreover, a double blind, randomized, placebo-controlled rechallenge trial in 34 patients with IBS where celiac disease was excluded, concluded that non-celiac gluten intolerance might exist [103]. It was found that overall symptoms, abdominal pain, bloating, satisfaction with stool consistency and tiredness were significantly increased in the group exposed to gluten compared to a control group. Furthermore, the study explored, but did not find any clues of underlying mechanism [103].

## 4 Summary of Study Background

Studies have shown that patients with CD in remission may have symptoms similar to those of IBS. The pilot study by Gearry *et al.* [19] found that a low FODMAP diet reduced adverse symptoms in this patient group. Importantly, most research on dietary interventions has focused on symptom relief in IBS patients. The mechanisms behind IBS are uncertain, however gastroenteritis leading to post-infectious IBS, alteration of the microbiota such as with small intestinal bacterial overgrowth have been suggested. CD share some of these features. An overview of some theoretical overlapping features between IBS and CD can be seen in table 4.

Table 4. Overview of some theoretical overlapping features of IBS and CD

<b>Feature</b>	<b>Theoretical overlaps</b>
Post-infectious IBS may be caused by preceding inflammatory insult, CD is an inflammatory disease	Inflammation, impaired barrier function, alterations in microbiota, stressful life events can contribute to flares, diarrhea is often a predominant symptom
Risk factors in developing IBS and CD	Smoking Increased risk after gastroenteritis Having a first degree relative with IBD
Symptoms in IBS and CD	Fatigue Musculoskeletal pain GI symptoms Symptoms similar to IBS in patients with CD in remission
The FODMAP approach	Reduction of dietary FODMAPs may reduce symptoms both in IBS and CD patients
Other	Small intestinal bacterial overgrowth is found in both IBS and CD Both conditions may affect HRQoL

Due to the possible common features of IBS and CD, findings from dietary interventions conducted on IBS-patients may be transferable to CD patients in remission with similar symptoms. The British Dietetic Association [104] has provided some guidelines for the

assessment of patients with IBS and these guidelines, or parts of it may also serve as guidelines for management of patients with CD.

Extraintestinal symptoms, such as fatigue and musculoskeletal pain are found in CD patients. There are limited studies on the efficacy on dietary interventions on these symptoms. In sum, knowledge about dietary interventions to reduce symptom severity in patients with CD in remission is needed.

## 5 Aims of the Study

The main aim of this study was to investigate if a dietary intervention low in proposed symptom triggers in IBS and allergens could reduce symptom severity in patients with CD in remission.

### 5.1 Specific Aims

The specific aims were:

1. To identify the most common self-reported food symptom triggers and symptoms at baseline.
2. To explore the possible mechanisms causing reactions to different food groups, including FODMAPs.
3. To compare and explore the severity of gastrointestinal and extraintestinal symptoms during alteration in the diet, from:
  - I. baseline to the end of a period of elimination diet, where foods suspected to trigger symptoms were excluded.
  - II. this elimination period to the endpoint of a reintroduction period with gradual reintroduction of suspected symptoms triggers.

## 6 Methods

### 6.1 Design and Patients

This study was based on an open prospective design.

Sixteen patients were included and completed the food- and symptom recall. A final sample of 12 patients completed the study intervention. Patients were recruited in the period September to December 2011 from Lovisenberg Diakonale Hospital and Oslo University Hospital, Ullevaal and Aker. They were also recruited through an advertisement on the Norwegian Association of Digestive Disorders' (Landsforeningen mot fordøyelsessykdommer) website ([lmfnorge.no](http://lmfnorge.no)) and advertisements at the University of Oslo campus sites, Domus Medica and Blindern.

#### 6.1.1 Inclusion Criteria

The inclusion criteria were age > 18 years, fluent in the Norwegian language, verified diagnosis of CD by a gastroenterologist (ICD-10 code K50 [105]) and CD in remission before entering the study indicated by calprotectin levels < 250 µg/ g feces as proposed by D'Haens *et al.* (2012) [42]. In addition, the patients were required to introduce foods containing wheat (if not diagnosed with celiac disease) and cow's milk products in the baseline period. Patients with colostomy, ileostomy or on steroids were excluded. One patient was found to be on Entocort after the study was completed and was not excluded.

### 6.2 Approvals

Approvals were given from the Department of Nutrition at the University of Oslo, Lovisenberg Diakonale Hospital and the Regional Committees for Medical and Health Research Ethics, see appendix 1.

## 6.3 Data Collection

### 6.3.1 Food- and Symptom Recall

The food- and symptom recall was completed by the patients at the introduction meeting. The food- and symptom recall had two purposes; to identify the patients' self-experienced food hypersensitivities and identify frequent food-items causing symptoms. First, they ticked off symptoms they commonly experienced, on the first page of the food- and symptom recall. These stated symptoms can be seen in table 5. The complete version of the food- and symptom recall handed out to the patients can be found in appendix 7. The following tables (5 and 6) are modified extracts of the complete version.

Table 5. The front page of the food- and symptom recall

<b>Gastrointestinal symptoms</b>	<b>Other physical symptoms</b>	<b>Psychological symptoms</b>
Retching	Swollen lips	Bad mood
Bloating	Rash/redness	Difficult concentrating
Frequent wind	Other swelling	Lethargy
Odorous wind/ feces	Palpitations	
Abdominal pain	Difficulty breathing	
Diarrhea	Itching	
Constipation	Headache/migrene	
	Musculoskeletal pains	

In the remaining pages of the food- and symptom recall, the patients were asked to identify food-items they experienced to initiate symptoms and the intensity, onset and duration of the symptoms. All known foods high in FODMAP, food-items 'not allowed' in Parker's elimination diet (appendix 10) and known common allergens were listed. A section from these pages is presented in table 6.

Table 6. A section from page two of the food- and symptom recall

Food-item	Do you eat this food-item?		Don't like/intolerant	Symptoms	Debut	Duration	Symptom intensity  (Enter 1,2,3 or 4, where 4 is the worst)
	YES	NO					
Apple							
Pear							
Artichoke							
Sugar snap peas							
Watermelon							
Honey							
Dried fruit							
Asparagus							
Canned fruit							
Brown cheese							
Cow's milk							

### 6.3.2 Daily Food- and Symptom diary

Every day throughout the study intervention the patients filled a semi-detailed food- and symptom diary with what they ate, mealtime and time of symptoms experienced. This diary was used to evaluate symptoms, symptom triggers, and compliance to the elimination diet and the reintroduction order. The food- and symptom diaries from the baseline period were used to prepare the reintroduction period. The patients were asked to report from seven different symptoms. The choice of these symptoms was based on a study conducted by Biesiekierski *et al.* [103]. The seven symptoms were; total symptoms, abdominal pain, bloating, abnormal feces (including both diarrhea and constipation), wind, fatigue and musculoskeletal pain. The food- and symptom diary can be seen in appendix 9.



### 6.3.3 Visual Analogue Scale

A visual analogue scale (VAS) was used to measure symptom severity of seven symptoms, the same as previously stated in the food- and symptom diary. The VAS was completed every evening of the study period. Patients were asked to place a mark on a line to signify where on this line his/her symptom severities were that day. Symptom severity was measured in cm, where 0 cm expressed; 'no symptoms' and 10 cm expressed; 'maximum symptom severity.' Data from the VAS was measured on the precision of 0.1 cm for every symptom, on every day, using a ruler (the same every time). A sample of the VAS is provided in appendix 8.

### 6.3.4 Blood Sample

One blood sample was collected from each patient during the study intervention. A sample was taken during baseline, for analysis of a routine medical test. This was used to evaluate if the patients had normal CRP, renal and hepatic function.

### 6.3.5 Fecal Test Measuring Calprotectin

Result from the most recent fecal-test taken before entering the study was collected. If the test had been conducted more than 12 months prior to entering the study, a new fecal test was completed before entering the study. A second fecal was then completed on day 29 (the day after the elimination period ended).

## 6.4 Study Intervention Procedure

Patients were invited to an introduction meeting where they were asked to complete the food- and symptom recall and a consent form. The following weeks were subdivided into three periods; baseline (two weeks), elimination period (two weeks) and an individual reintroduction period (four to nine weeks). The blood sample was taken during the baseline period and a fecal test was taken the day after the elimination period. The VAS and the food- and symptom diaries were to be completed every day during the intervention. The study timeline is illustrated in figure 5.

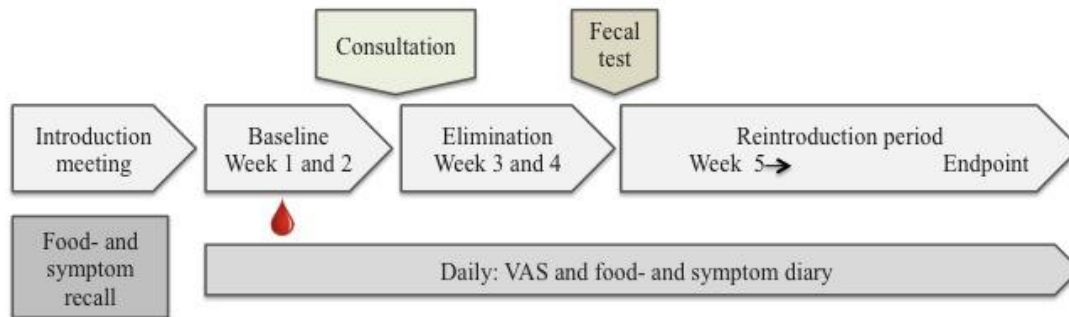


Figure 5. Study timeline

#### 6.4.1 Introduction Meeting

Recruited patients were invited via a phone call and e-mail to an introduction meeting at Lovisenberg Diakonale Hospital. If they met the inclusion criteria and agreed to participate, they were asked to complete a detailed food- and symptom recall (appendix 7) and to read and sign a consent form. A copy of the consent form can be seen in appendix 3. The patients were given identification numbers to ensure anonymity during the study. Information about the food- and symptom diary and VAS was also given. It was emphasized that the two forms had to be completed every day throughout the study intervention period. The invitation sent to the patients and the power point slides used in the introduction meeting can be seen in appendices 2 and 4, respectively.

#### 6.4.2 Baseline Period

After the introduction meeting the patients were asked to follow their habitual diet for two weeks. This was called baseline. As many patients may exclude food-items without follow-up from health staff, we wanted to see how severe symptoms could be when these patients included food groups that are common in the Norwegian diet. Hence, the patients were asked to include foods containing wheat and cow's milk. The patients sent in copies of the completed food- and symptom diaries and VAS on day three during this period to ensure correct understanding and completion of the forms. VAS was also used to review if the patients had food hypersensitivities before they were included further in the study.

### 6.4.3 Individual Consultation

The day after baseline, at day 15 during the intervention, the patients were called in for an individual consultation with the master student. They met individually at Lovisenberg Diakonale Hospital, Oslo. The elimination diet, the reintroduction period, VAS and food- and symptom diary were discussed. The following measurements were taken; weight, height and their body mass index (BMI) was calculated. Furthermore, they were given information about the home fecal test for analysis of calprotectin levels in feces.

### 6.4.4 Elimination Period

After the baseline period, the patients were asked to follow the prepared elimination diet for two weeks. The British Dietetic Association have provided guidelines for dietary management in IBS and implies that an elimination diet should be followed for two to four weeks to detect a possible symptom improvement [104]. As this study had limited time resources, and a period of two weeks was set. The foods allowed in this elimination diet were based on two different approaches that have been indicated as treatments for food hypersensitivity in patients with IBS. The first was a modified exclusion diet used by Parker *et al.* (1995) [4], and is based on the most common food-items patients with IBS reported adverse symptoms towards. This exclusion diet has been suggested as a treatment for food intolerance in IBS in the nutrition textbook 'Human Nutrition,' 12<sup>th</sup> edition [106]. The main components of this exclusion diet can be seen in appendix 10. The second approach was the low FODMAP diet developed at Eastern Clinical School, Monash University [3]. A study conducted on patients with fructose malabsorption and IBS found that 74% responded positively to this low FODMAP diet. An overview of a low FODMAP guide is provided in appendix 11. Foods low in FODMAP and foods allowed in Parker's modified exclusion diet were the basis of the elimination diet used in the present study. Importantly, common food allergens such as milk, eggs, tree nuts and peanuts were also eliminated [66]. Fish, shell fish and soya are considered major food allergens [66], but was allowed if no allergic hypersensitivity to these food-items was previously diagnosed. All foods allowed during the elimination period are presented in table 7.

Table 7. All foods allowed during the elimination period

<i>Cereals</i>	<i>Vegetables</i>	<i>Fruit &amp; Berries</i>	<i>Spices</i>	<i>Beverages</i>
Buckwheat	Broccoli (<1/4 /day)	Avocado (1/4 /day)	Chili	Boiled water
Plain rice	Brussel sprouts	Banana	Pepper	Bottled water
Puffed rice	Cabbage	Blueberries	Salt	
Quinoa	Carrot	Cantaloupe	Sugar (limited)	
Rice cakes	Celery	Grapes		
Rice noodles	Cucumber	Honey dew melon	<i>Fat sources</i>	<i>Miscellaneous</i>
	Eggplant	Kiwi	Canola oil	Baking soda
<i>Meat &amp; Fish</i>	Fennel (<1dl/day)	Passion fruit	Olive oil	Olives
Bacon	Ginger	Pineapple		Sunflower seeds
Chicken	Lettuce	Rhubarb		
Fish, all kinds	Parsnip	Star fruit	<i>Fresh herbs</i>	<i>Milk substitute</i>
Game	Peas (<0.5dl/day)	Strawberries	Basil	Rice milk
Ham	Spinach		Chives	Soya milk
Pork	Spring onion(green part)		Coriander	
Shellfish	Squash		Parsley	
Tofu	Swede		Rosemary	
Tuna in brine	Sweet potato(<1dl/day)		Thyme	
Turkey	Turnip			

Elimination diet prepared by the author, 2011.

If the patients suspected any foods that were included in the prepared elimination diet (table 7.) to cause symptoms, that food-item(s) was also excluded. Patients received suggestions for meals and recipes prepared by the author, see appendix 6.

#### 6.4.5 Reintroduction of Food-items

After adhering to the elimination diet for two weeks the patients reintroduced a food-item every other day. The patients were given a suggested order of food-reintroduction via email approximately a week before the reintroduction period began. They were then able to request changes, such as restructuring the reintroduction order. Reintroductions of food-items were tailor-made to the individuals based on the food- and symptom recall and the daily- food and symptom diary filled in during the baseline period. This reintroduction period was influenced by the patients' feedback, and this may have empowered the patients to control their symptom outcome and may lead to a diet with fewer symptom triggers. The reintroduction period started with foods suspected not to cause reactions. If a reaction occurred, the patient returned to the diet when he/she was symptom-free or had adequate symptom control, and started the reintroduction period again with next food-item on the reintroduction plan. The reintroduced food-items were consumed in normal portions for at least two meals on the planned day. All patients were asked to reintroduce five different FODMAP-sources; including wheat and cow's milk products. A sample of one patient's reintroduction form can be studied in appendix 12.

#### 6.4.6 Statistical Analyses

Results from the collected data were analyzed using SPSS (version 19.0). Since this was an explorative study and there was insufficient background data, it was not attempted to formally calculate sample size. Values are reported as medians and interquartile intervals unless otherwise stated. The data was not normally distributed. The non-parametrical Wilcoxon signed rank test was used to find differences in symptom severity using the VAS data, from baseline to the elimination period and from the elimination period to the reintroduction endpoint. A  $P < 0.05$  indicates statistical significance.

## 7 Results

### 7.1 Sample Characteristics

A total of 53 patients responded to the study invitation. Of those, 19 patients did not meet the study inclusion criteria. The remaining 34 patients were invited to an introduction meeting. Sixteen patients agreed to participate, however four patients withdrew during the study intervention. In the end, 12 patients completed the study. The recruitment, exclusion and withdrawal pathway are illustrated in figure 6.

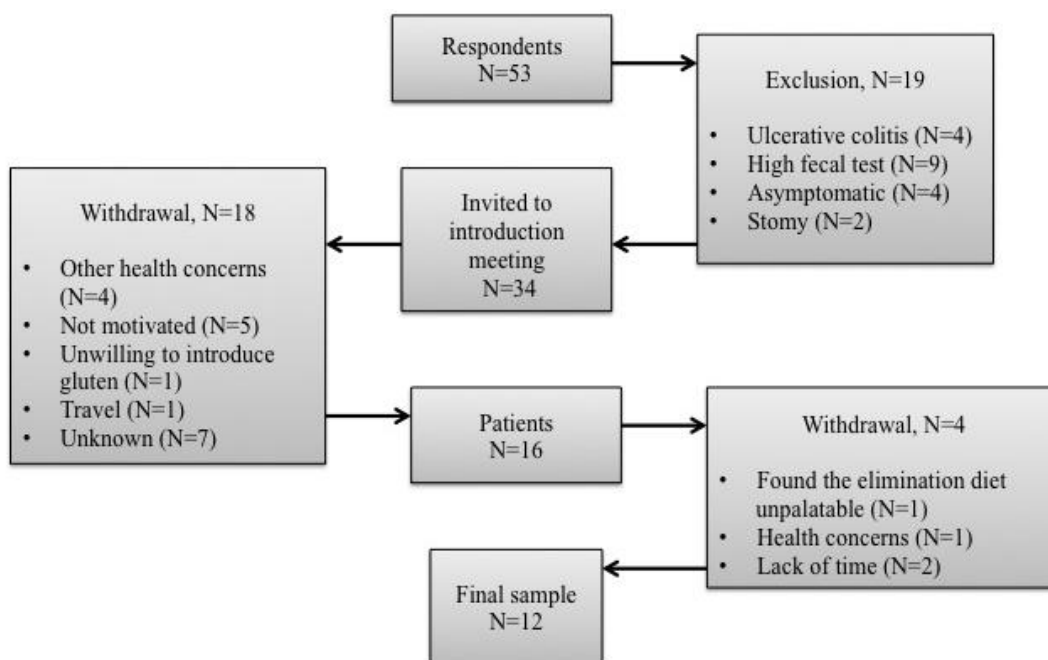


Figure 6. Recruitment pathway and reasons for withdrawal and exclusion

Of the final sample, two patients did not fill in the requested forms (VAS and food- and symptom diary) during the reintroduction period. All patients had normal CRP and adequate renal and hepatic function assessed with blood biomarkers. An overview of the biomarker values from the routine medical test analyses can be found in appendix 13. One patient had anemia and was treated accordingly during the study period. Furthermore, one patient had Bechterew's disease, one had celiac disease and one was on a sick leave due to severe fatigue. The patient with celiac disease did not include wheat in the study period.

As presented in table 8, the calprotectin analyses, based on fecal samples provided by the patients after the elimination period (day 29), found that five patients were still in remission during the study intervention. However, two tests were completed, but not suitable for analysis. Results from two patients were lost. Two patients had elevated calprotectin levels (>250 µg/ g in feces).

Table 8. Characteristics of the 12 patients completing the study intervention

Patient no.	Age	Gender *	BMI **	Stenosis or surgery	Year of diagnosis	Disease location	Drug therapy	Calprotectin in feces	
								Before study	During study
1	28	F	25.6	No.	2007	Terminal ileum	No.	< 20 µg/g	20 µg/g
2	26	F	25.0	Resection (3 cm of terminal ileum, 2010)	2009	Terminal ileum	Entocort	60 µg/g	NA
3	47	F	24.1	Some stenose in terminal ileum	2001	Terminal ileum	Pentasa	22 µg/g	NA
4	35	F	16.7	No.	2010	Colon and terminal ileum	No.	43 µg/g	24 µg/g
5	45	M	27.4	No.	2010	Colon and terminal ileum	No.	162 µg/g	83 µg/g
6	23	F	23.0	No.	2011	Small intestine	Imurel	47 µg/g	NA
7	30	M	22.5	Resection (5 cm of ileum, 2002)	2002	Terminal ileum	No.	158 µg/g	NA
8	39	M	22.0	No.	2000	Colon	Methotrexate	33 µg/g	20 µg/g
9	66	F	20.0	No.	2010	Colon	No.	46 µg/g	<b>1424 µg/g</b>
10	26	F	24.0	No.	2007	Colon	No.	< 20 µg/g	233 µg/g
11	44	F	24.8	No.	2011	Colon	No.	187 µg/g	<b>347 µg/g</b>
12	42	M	26.3	No.	2007	Terminal ileum	No.	213 µg/g	NA

Age is presented in years. \*M, male, F, female, \*\*Body Mass Index, presented as kg/m<sup>2</sup>

NA, Not available or lost calprotectin values. Calprotectin levels in feces > 250 µg/ g are shown in bold.

Furthermore, according to the BMI-classification provided by the World Health Organization [107] one patient was classified as underweight ( $BMI < 18.5 \text{ kg/m}^2$ ) and three patients were classified as overweight ( $BMI > 25 \text{ kg/m}^2$ ). Three patients were on drug therapy and two patients have had intestinal resection. One had some stenosis in the distal small intestine. The most common site of the CD was the colon and the terminal ileum.

## 7.2 Symptoms and Symptom Triggers Reported at the Introduction Meeting

Sixteen patients completed the food- and symptom recall at the introduction meeting. Figures 7 and 8 present findings from the recall; the most common self-reported symptoms and most common food-items to provoke symptoms in general. As seen, all 16 patients reported wind and abdominal pain as one of their most common symptoms. Additionally, 15 patients reported bloating, 14 patients reported odorous wind/feces and diarrhea and 12 patients reported fatigue as their one of their most common symptom.

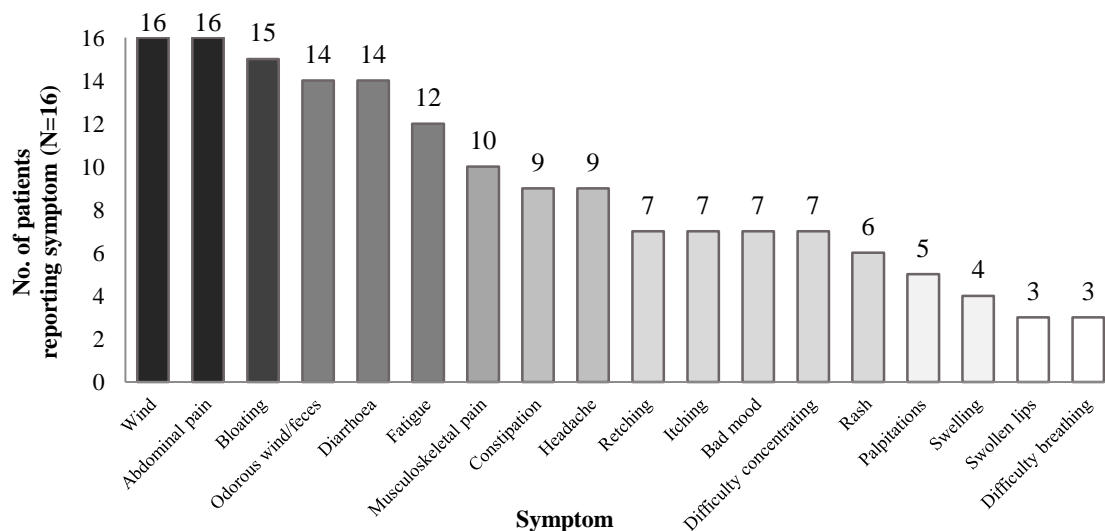


Figure 7. Frequency distributions showing the various symptoms reported by the patients at the introduction meeting

Figure 8 shows the most common food-items reported to trigger adverse symptoms. The most common symptom triggers were cow's milk (13 of 16), wheat and apple (11 of 16) followed by ice cream, pasta, pear, rye, sugar free gums/mints and wheat buns (10 of 16).



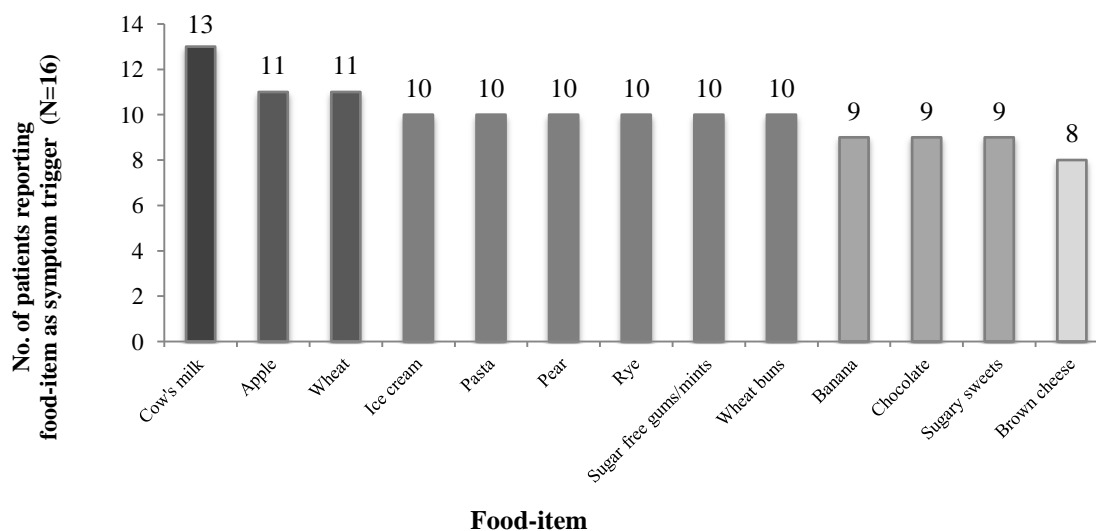


Figure 8. Food-items reported at the introduction meeting as symptom triggers, by more than 50% of the patients

An overview of the number of patients who reported a reaction to the different dairy products listed on the food- and symptom recall is presented in table 9. After cow's milk, the Norwegian brown cheese<sup>2</sup> was the most common dairy product to trigger symptoms. Fermented sour milk and white Gouda cheese only produced adverse symptoms in four and three patients.

Table 9. Number of patients reporting a reaction to the various dairy products

Dairy product	No. of patients
Cow's milk	13
Norwegian brown cheese	8
Custard	7
Yoghurt	6
Fermented sour milk	4
White Gouda cheese	3

Some food-items listed on the food- and symptom recall were never or rarely reported as symptoms triggers. For example, none of the patients reported reactions to white/red fish, sweet potatoes or blackberries. Some food-items were reported to cause symptoms in one patient only, such as watermelon and avocado. An illustration of all the food-items listed on

<sup>2</sup> Norwegian cheese made of whey in the cow-or goat's milk. Also called Norwegian fudge cheese or caramelized brown cheese. In Norwegian it is called '*brunost*.'

the food- and symptom recall and the number of patients who reported reactions can be seen in appendix 15.

### 7.3 Symptom Change Between the Different Intervention Periods

Three time periods were used to evaluate changes in symptom severities; the baseline, the elimination and the reintroduction period. Baseline week two had the highest frequency of symptoms compared to baseline week one; hence baseline week two was used for further evaluation. Elimination week two had the lowest frequency of symptoms compared to elimination period one; hence elimination week two was used for further evaluation. The duration of the reintroduction period differed among the patients (range 4 to 9 weeks) depending on how many food-items they reintroduced. The last period presented is the last reintroduction week, which denoted the endpoint.

As the patients had to include food-items they may have excluded on their own before entering the study, the symptoms may have worsened as they included those food-items throughout the baseline period. Consequently, the second week of the baseline period had the highest frequency of symptoms in most (7 of 12) of the patients. Furthermore, symptom relief may not occur instantly when starting an elimination diet, as the possible adverse reactions from baseline may need some time to ‘wash out.’ In line with this, most (9 of 12) patients had the lowest frequency of symptoms in the elimination week two.

The patients were requested to tick of their experienced symptom severity at the VAS every day during the study intervention. The mean value of the seven recordings obtained during one week was then calculated for each patient. Then the median value and the interquartile range based on these mean values obtained from the 12 patients were calculated. As expected, there was a significant decline in symptom severity in all symptoms from baseline week two to elimination week two (table 10). Unexpectedly, no significant change was found from elimination week two to the endpoint. The values are presented in table 10.

Table 10. VAS recordings of symptom severity obtained during the second weeks of the baseline and elimination periods and at the endpoint

	Baseline week two	Elimination week two	P-value*	Endpoint	P-value**
Total symptoms	4.1 (1.2-8.8)	2.3 (0.4-4.8)	< <b>0.01</b>	2.1 (0.7-4.2)	0.76
Abdominal pain	2.3 (0.6-7.4)	0.8 (0.2-2.6)	<b>0.01</b>	1.0 (0.0-4.2)	0.29
Bloating	3.3 (0.9-7.6)	0.7 (0.0-4.8)	< <b>0.01</b>	1.4 (0.0-3.9)	0.68
Abnormal feces	3.4 (0.0-7.4)	1.0 (0.0-3.8)	<b>0.02</b>	1.1 (0.0-3.3)	0.96
Wind	3.5 (0.8-7.1)	0.9 (0.3-3.7)	< <b>0.01</b>	1.8 (0.4-4.1)	0.44
Fatigue	3.3 (0.0-7.6)	2.6 (0.0-4.9)	<b>0.03</b>	1.3 (0.0-3.6)	0.29
Musculoskeletal pain	3.3 (0.0-7.9)	1.4 (0.0-4.3)	<b>0.03</b>	0.6 (0.0-4.1)	0.16

Values are the median (range) of the VAS recordings from the 12 patients (10 patients at endpoint). Statistically significant results are shown in bold. \*P-value for comparison of VAS from baseline week two to the elimination week two. \*\* P-value for comparison of VAS from elimination week two to the endpoint.

## 7.4 Illustrations of Symptom Change

The subsequent figures 9 to 15 were prepared to illustrate the results presented in table 10. To improve the overall picture of the symptom severities at the different time periods, the recordings obtained from baseline week one and elimination week one were also included in the following figures.

The figures demonstrate the 25<sup>th</sup>, 50<sup>th</sup> (median) and 75<sup>th</sup> percentiles of the symptom severities scored at the VAS. Seven symptoms are illustrated below: total symptoms, abdominal pain, bloating, abnormal feces, wind, fatigue and musculoskeletal pain. Each figure is separated into five periods; baseline week one, baseline week two, elimination week one, elimination week two and the endpoint (the last week of the reintroduction period).

### 7.4.1 Total Symptoms

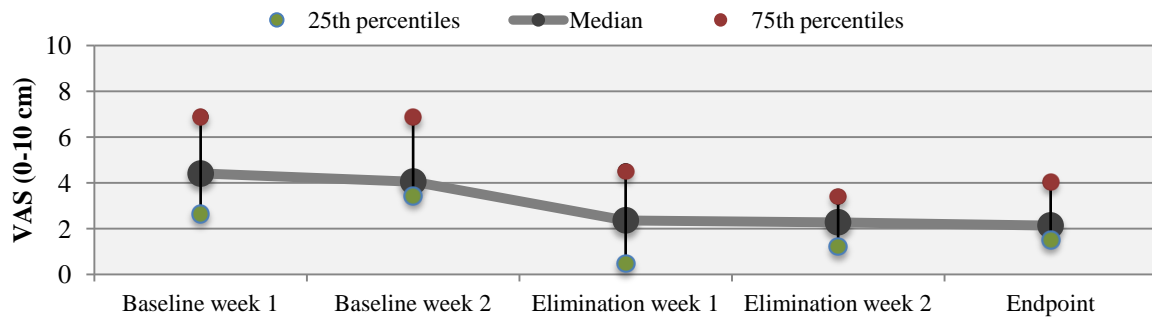


Figure 9. Median change in total symptoms with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

As illustrated above, total symptoms declined ( $P < 0.05$ ) from baseline to the elimination period and remained fairly constant ( $P > 0.05$ ) until the endpoint. This implies that total symptoms did not increase, even when suspected food symptom triggers were reintroduced.

### 7.4.2 Abdominal Pain

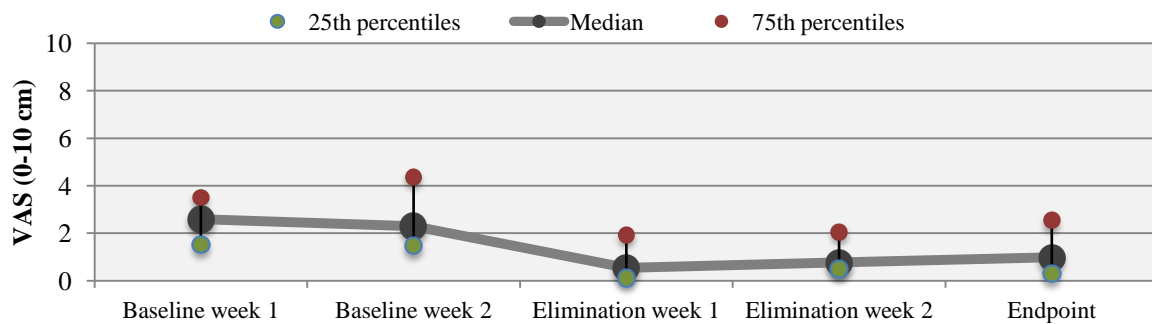


Figure 10. Median change in abdominal pain with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

Abdominal pain declined ( $P < 0.05$ ) from baseline to the elimination period, and then abdominal pain increased insignificantly to endpoint.

### 7.4.3 Bloating

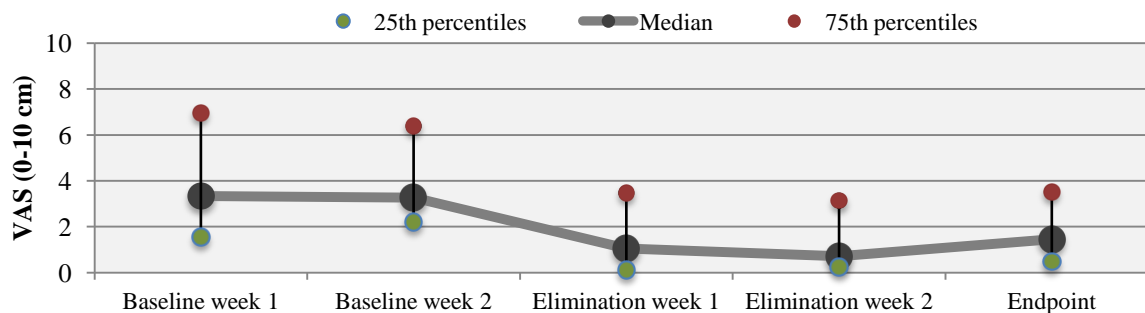


Figure 11. Median change in bloating with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

The symptom severity of bloating decreased significantly from baseline to the elimination period, and then increased insignificantly from elimination to endpoint.

### 7.4.4 Abnormal Feces

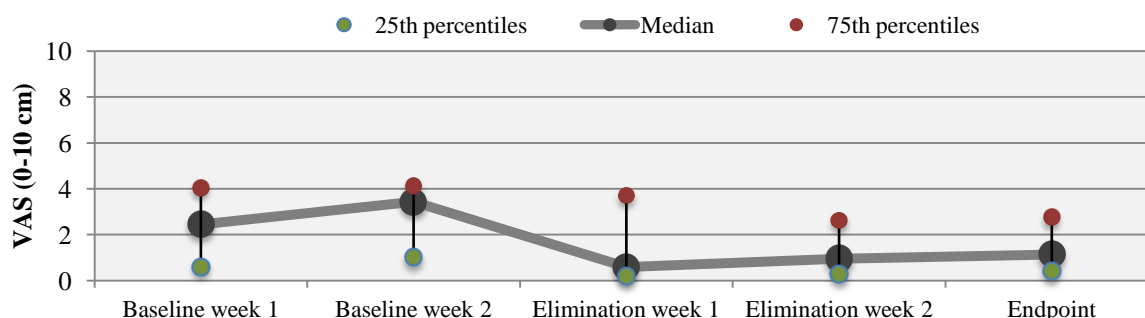


Figure 12. Median change in abnormal feces with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

Notably, the symptom severity abnormal feces was most frequent at week two compared to week one during the baseline period. The severity decreased significantly towards the elimination period. It seemed like abnormal feces increased slightly, but not significantly from the week one of the elimination period to week two of the elimination period, perhaps because some patients reported constipation in this period. A small, but insignificant increase in symptom severity was seen from the elimination period to the endpoint.

### 7.4.5 Wind

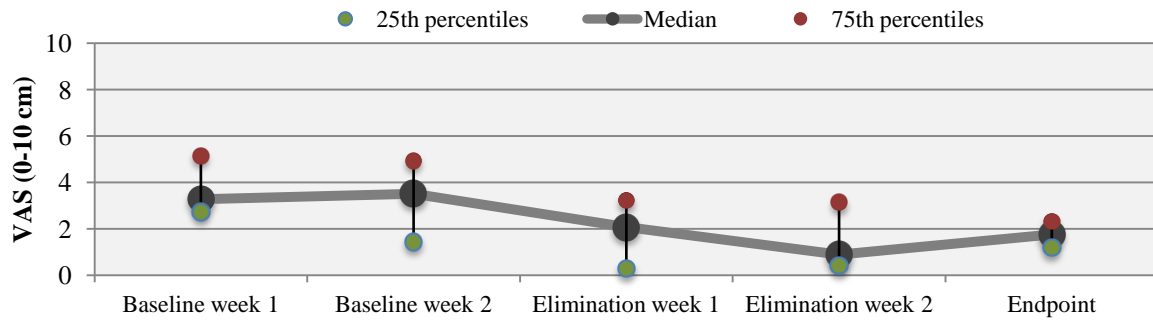


Figure 13. Median change in wind with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

The symptom severity of wind decreased significantly from baseline to the elimination period and then had a small, insignificant increase to the endpoint.

### 7.4.6 Fatigue

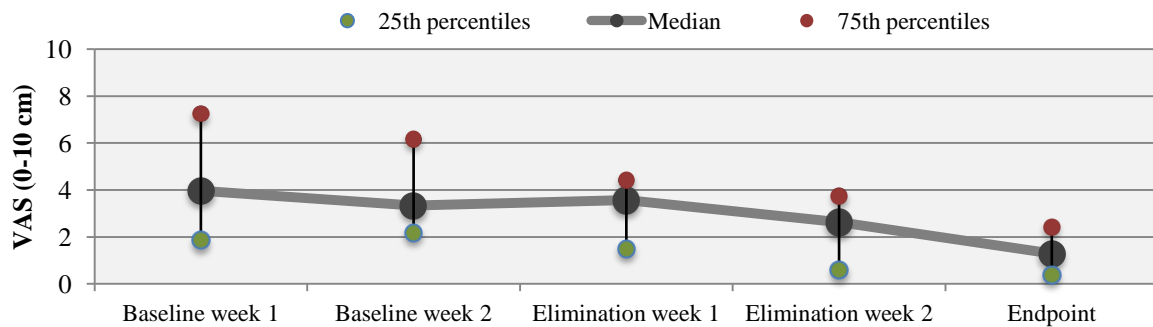


Figure 14. Median change in fatigue with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

The reported severity of fatigue seemed unchanged from baseline to the first week of the elimination period and decreased significantly after the second week of the elimination period. Moreover, fatigue decreased insignificantly from the elimination period to the endpoint. As illustrated, reported fatigue seemed to be lower at endpoint than during the elimination period. This suggests that the symptom relief in fatigue caused by the elimination diet may have a late onset.

### 7.4.7 Musculoskeletal Pain

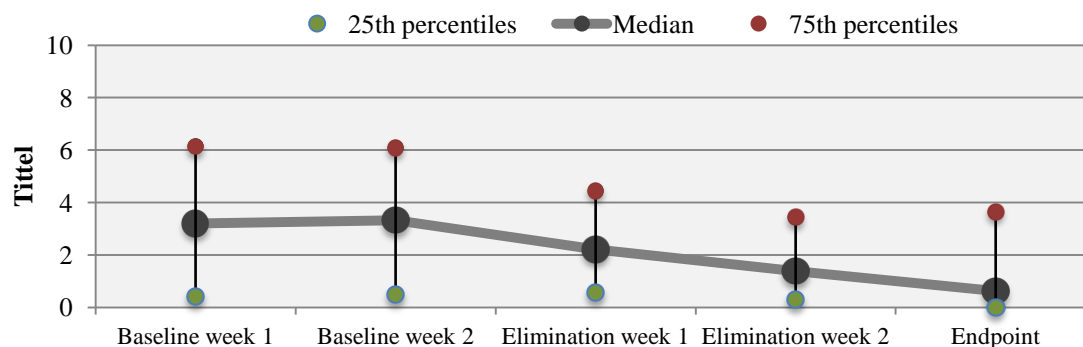


Figure 15. Median change in musculoskeletal pain with upper (75<sup>th</sup>) and lower (25<sup>th</sup>) percentiles

Musculoskeletal pain declined significantly from baseline to the elimination period and declined thereafter insignificantly until the endpoint. This suggests that musculoskeletal pain may be a slow responding symptom to the elimination diet, with the same features as fatigue.

In summary, figures 9-15 illustrate that there was a decrease in total symptoms as well as the various specified symptoms from baseline to the elimination period. Interestingly, fatigue and musculoskeletal pain also had a continued insignificant decrease from the elimination period to the endpoint which were not seen in the other symptoms. However, wind, bloating and abdominal pain seemed to increase slightly, but insignificant from the elimination period to the endpoint.

Notably, there were major differences in symptom severity reported each day at the VAS. An example of one baseline week in one patient is provided in appendix 16, to illustrate how different the days in one week could be. Furthermore, it seemed like one patient did not respond to the elimination diet. The other 11 patients commented that they had found a diet which caused fewer symptoms than before the study intervention. In addition, most patients reported that their knowledge about what food-item(s) causing a reaction had been enhanced during the intervention. To illustrate a patient who responded to the elimination diet and the one patient who did not respond, a comparison is provided in appendix 17.

## 7.5 Symptom Triggers Reported from the Reintroduction Period

The reintroduction of food-items was individually planned based on the patient's dietary habits and the food-and symptoms diaries. Because of this, the patients reintroduced a variety of different food-items and these food-items were thus grouped. The food group 'wheat products' includes pasta, bread and buns made from wheat. Cow's milk products include all products made from cow's milk, such as yoghurt and milk. Legumes refer to beans, lentils and chickpeas. The food group called 'fruit with excess fructose' refers to e.g. mango, apple, and pear. These fruits have a higher concentration of fructose relative to glucose [87]. Coffee and black tea are called caffeine beverages. Some food groups were found to cause reactions more frequent than others. Figure 16 shows the most common food groups that caused adverse symptoms during the reintroduction period.

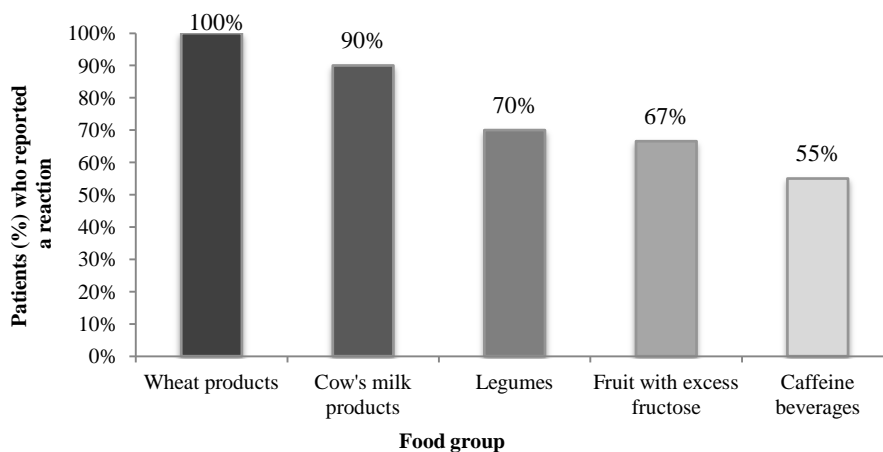


Figure 16. Most common food groups to cause symptoms

Figure 16 indicates that wheat products caused reactions in all patients who introduced a food-item from this group. Two patients suspected that foods containing gluten made them ill during the baseline period and refused to reintroduce gluten-containing foods, such as wheat products. One patient was diagnosed with celiac disease and was not requested to eat wheat products during the intervention period. Two patients did not introduce cow's milk products because of fear of adverse symptoms. Of the 10 patients introducing cow's milk products, nine reported a reaction. Ten patients introduced legumes and seven reported a reaction. All patients reintroduced fruits with excess fructose and eight patients reported a reaction. Caffeine beverages caused symptoms in 6 of 11 patients.



## 8 Discussion

### 8.1 Limitations and Strengths

#### 8.1.1 Characteristics and Quality of Sample

Similar studies are lacking and sample size was hence not calculated. We aimed for a final sample of 20 patients, but this was proved difficult. The final sample size of 12 patients was rather small and there was no control group, hence the results should be considered carefully. The most common reported reasons for withdrawal were lack of motivation and other current health related concerns. Some expressed fear of developing adverse symptoms during the study intervention and several patients reported that they 'felt too tired' to participate. Of the 12 patients in the final sample, 10 were recruited from Lovisenberg Diakonale Hospital. These patients may have felt obliged or motivated to participate as their gastroenterologist took part in this project. However, recruitment from other hospitals and from advertisements did not commence before October/November 2011. Consequently, the time spent on recruitment of patients from elsewhere than Lovisenberg Diakonale Hospital was limited as the recruitment period ceased 1 January 2012. Moreover, it cannot be excluded that the patients completing this study were more motivated and concerned about health than those who withdrew or possibly decided not to volunteer for study participation. Unfortunately, we have limited information about the patients who withdrew from the study.

The general gender rate in CD is approximately equal [50]. However, in the present study the distribution was somewhat uneven. Of the 34 patients invited to the introduction meeting, 26 were female, and of the 12 patients completing the study intervention, eight were female. The calculated BMI of the 12 patients ranged from 16.7 to 27.4 kg/m<sup>2</sup>. One patient was found underweight (BMI 16.7 kg/m<sup>2</sup>), however she reported that her weight had been stable for a long period. Three patients were moderately overweight and their BMI ranged from 25.6 to 27.4 kg/m<sup>2</sup>. Three patients were on drug therapy. Furthermore, five patients had terminal ileal CD, four had colonic CD, two had colonic and small intestinal CD and one had small intestinal CD only. Location of the CD may affect e.g. malabsorption of lactose. The possible association between intestinal location of CD and susceptibility to some underlying mechanisms and/or symptom features was not covered in this study, but requires further exploration.

In previous studies, the Rome criteria or specific questionnaires have been used to define if CD patients have symptoms similar to IBS [15, 82]. The present study did not use a specific tool to define symptoms before the patients were included. In this study, a gastroenterologist identified patients with self-reported hypersensitivities even if in remission, during their consultation at the hospital and they were then recruited to the study. The symptom severities reported at the VAS during the baseline period were also reviewed to find if they experienced symptoms before the patients were included further. One patient was found to be asymptomatic and was excluded during the baseline period. It cannot be ignored whether some of the patients had IBS according to the Rome criteria, in addition to CD. Furthermore, fatigue and musculoskeletal pain were not objectively diagnosed. However, the purpose of this study was not to identify the mechanisms underlying fatigue and musculoskeletal pain, nor to find if the patients had an IBS diagnosis, but to explore the efficacy of the dietary intervention on self-reported food hypersensitivity.

There were some differences in the definition of remission of CD in previous studies on IBS-like symptoms. One study defined remission by the Crohn's disease activity index [15], which is not so commonly used today. In another study remission was defined by clinical measurements and judgment from a physician [82]. Notably, analysis of calprotectin levels in feces, as used to evaluate and include patients with CD remission in the present study, is regarded as the best marker of remission available today [42].

### 8.1.2 Methodological Considerations

A double-blind placebo-controlled food challenge has been considered the 'gold standard' of food reintroduction and for diagnosis of food hypersensitivities [108]. This procedure may be expensive and time-consuming to carry out. Moreover, the value of a double-blind placebo-controlled food challenge has been 'disputed' and is rarely performed today [109].

Furthermore, a hypersensitivity reaction has been defined as '*objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects*' [6]. It seems however almost impossible for a capsule to include doses of a symptom trigger comparable of the dose found in food-items or even in a meal. This study used an open re-challenge of food-items, consistent with the procedure in Parker *et al.* [4]. However, Parker *et al.* used a standardized order of food reintroduction. In this study the patients reintroduced food-items based on their individual dietary habits and self-reported reactions. Importantly, there were some similarities in the reintroduction of food-items for all the patients. They were

all asked to reintroduce five different FODMAP sources, which also included cow's milk- and wheat products, which are known to frequently cause adverse symptoms both in IBS and CD. A new food-item was introduced every other day during the reintroduction period. The disadvantage with this choice of time span may be that possible delayed adverse reactions to food-items can be difficult for the patients to identify.

It has been suggested that the use of hydrogen breath tests, to identify lactose and fructose should be implemented in the assessment of food hypersensitivities when available [3]. These tests could have identified malabsorption of these carbohydrates before starting the study intervention. It has also been proposed that lactulose breath tests to identify small intestinal bacterial overgrowth should be assessed before carbohydrate malabsorption, as small intestinal bacterial overgrowth can generate a falsely abnormal result of malabsorption [34]. However, the present study did not have the resources to implement these tests.

The most common symptoms reported by the patients at the food- and symptom recall at the introduction meeting were wind, odorous wind, bloating, diarrhea, fatigue, abdominal pain, itchiness, musculoskeletal pain and constipation. These are consistent with the symptoms chosen for the VAS and food- and symptom diary used to collect data throughout the study intervention. Notably, diarrhea and constipation were joined together as the term 'abnormal feces' and itchiness was not included.

Self-reported symptoms can be vague and difficult to measure based on patients' descriptions. VAS was chosen for data collection of symptom severities as it is considered to be a useful tool for translating patients' subjective symptoms into numerical data [110]. VAS has been used by several studies to measure severity of symptoms [18, 103, 110]. In a study by Biesiekierski [103], symptom severities at VAS were obtained only by the end of each week during the intervention they performed. Arguably, it may be difficult for patients to recall how severe their symptoms have been the past seven days. Because of this, we decided to calculate the weekly VAS value from the seven recordings obtained during one week, and these values may hence be more accurate. This may also be useful as the symptom severities were found to change from day to day, as seen in appendix 15. If we e.g. had evaluated differences in symptom severities from the values reported at one day only during each intervention period, the results would be highly dependent on the days chosen. By comparing the symptom severities from week to week, it may be easier to detect true differences over time.

The forms used in this study, the food- and symptom recall, VAS and food- and symptom diary may not have included all symptoms or food-items. Due to this, some information about this patient group may have been left out. Still, most of the patients reported that their most common symptoms were stated at the forms. Furthermore, the patients may interpret the symptom terminology used differently, especially regarding fatigue and musculoskeletal pain, which may have been unfamiliar to some of the patients before entering the study intervention. However, the meaning of the terms was carefully explained at the introduction meeting.

Social and personal factors may have affected the reported symptom severities.

Unfortunately, we were not able to control for these factors. This could have been done by e.g. recording the patients' HRQoL during the study intervention period. However, some factors were outside our control. For example, the patients were given information about the study procedure before starting the intervention. This may have created some expectations of symptom relief and favor an expected outcome. The patients' previous adverse experiences to food intake may also have influenced the reported symptom severities. Furthermore, the patients had to include food-items during the baseline period that some patients may have excluded prior to the study, possibly because of adverse reactions. Consequently, the symptom severities at baseline may be misleadingly high. The elimination diet also required planning of meals and attention to dietary intake. This may have improved the patients' eating habits, leading to decreased symptom severities. A major strength of the study procedure was that the same person provided information to the patients.

Unfortunately, the elimination diet had one error that could have affected the symptom severities: The elimination diet handed out to the patients included the food-item 'cabbage,' which is excluded on the low FODMAP diet and hence should have been excluded in the elimination diet used in this study. Still, when examining the patients' food-and symptom diaries, none of the patients included cabbage in their diet in this period.

### 8.1.3 Compliance

Individual interpretations of the information given to the patients at the information meeting and at the individual consultations can be affected by the patients' health literacy, such as educational level and health related education/ work. This may have affected compliance to the elimination diet and accuracy of the reported symptom severities. Unfortunately, two patients did not hand in VAS and food- and symptom diaries from their reintroduction period. This may have been prevented if the patients had been called in for an individual consultation before starting the reintroduction period, in addition to the one they had before the elimination period.

Inevitable, when conducting a clinical study, unexpected situations may occur. For example, one patient experienced death in near family and one patient had a two-day hospital stay due to anemia during the study intervention. All patients followed the elimination diet (according to the food- and symptom diaries), except for one patient who had one meal with foods that were not allowed in the elimination diet. However this patient's elimination period was extended to 'wash out' this meal. Furthermore, many common staple foods were excluded during the elimination diet and in phases of the reintroduction period. This could have caused some social difficulties for the patients. Several patients reported that they lost their motivation during the end of the reintroduction period.

Moreover, some information about the study sample became incomplete: Five patients did not provide samples or provided inadequate samples for analysis of calprotectin in feces during the study intervention. Any ongoing inflammation during the study intervention in these five patients is therefore unknown, but is unlikely, as they did not report any complaints consistent with inflammation. Importantly, two patients were found to have elevated calprotectin levels during the study intervention, and this may have influenced the reported symptom severities as inflammation may cause GI symptoms like diarrhea. Furthermore, some biomarker values from the routine medical test were not analyzed in some patients (appendix 13). In retrospect, we noticed that the number of collected biomarkers in the routine medical test should have been standardized before the study was conducted. This error has consequently led to some missing biomarker values in some patients.

A major strength of the current study was that the patients were provided with suggestions for meals and recipes for the elimination period. This may have made it easier for the patients to

follow the elimination diet and conquer social difficulties. In the study by Barret *et al.* (2009), investigating the efficacy of the low FODMAP diet on adverse symptoms in patients with CD, reduction in overall symptoms and adherence to the low FODMAP diet were greater in patients who used the cookbooks they were provided [19].

## 8.2 Implications from the Study Intervention

The main aim of this study was to investigate if the dietary intervention used could reduce symptoms. We found that total symptoms as well as the various specified symptoms significantly declined when diet was altered. In addition, symptom severity did not increase significantly from the elimination period to the study endpoint. This was unexpected as food-items were gradually reintroduced, and suspected symptom triggers such as cow's milk and wheat products often were introduced at the end of this reintroduction period. This may indicate that the patients managed to identify and exclude the food symptom triggers, and that they found an individualized diet with adequate symptoms. The extraintestinal symptoms seemed to have a delayed response to the dietary alteration compared to the more immediate response found in the GI symptoms. These symptoms and possible mechanisms causing these symptoms are discussed further in the next section. Some food groups were found to trigger reactions more frequently than others, and it was found that the most common symptom triggers were cow's milk products, wheat products, fruits with excess fructose and caffeine beverages. In the following section, the compounds in these food groups that could have possibly caused the adverse reactions will be discussed.

### 8.2.1 Food groups that caused adverse reactions and possible mechanisms

The present study aimed to identify the most common food groups to cause adverse symptoms. It was found that there was consistency from the reported symptom triggers collected at the introduction meeting and the food-items reported to cause symptoms during the reintroduction period. This implies that the first line dietary assessment of these patients may give some clues on what dietary alterations that may be useful. To sum, the most frequent food groups to trigger symptoms were cow's milk products e.g. cow's milk and ice cream, wheat products e.g. wheat flour, wheat buns, pasta and fruits with excess fructose e.g. apples and pears. Rye was also one of the most common symptom triggers reported at the introduction meeting, but was not frequently reintroduced. Legumes were only reported as

frequent symptom triggers during the reintroduction period, possibly because legumes are not widespread in a common Norwegian diet. Cow's milk and wheat have been reported as common symptom triggers in patients with IBS and CD in previous studies [4, 111]. The compounds found in these food groups that possibly caused the adverse reactions in this study are discussed henceforth.

### *The FODMAP approach*

The most frequent food groups to trigger symptoms in this study were cow's milk products, wheat products and fruits with excess fructose. These three food groups contain the fermentable carbohydrates; lactose, fructans and fructose. These carbohydrates are recently referred to as FODMAPs. Hence, these FODMAPs may have contributed to the adverse reactions found in this study. Lactose malabsorption has been found frequently in patients with CD [95]. Reactions to wheat products are often associated with reactions caused by the protein in wheat products, but may be caused by the high content of the carbohydrate fructan [87]. Furthermore, fructose malabsorption has been indicated more frequently in patients with CD compared to healthy controls [95]. Some fruits with excess fructose such as apples and pears also contain sorbitol and mannitol, which are polyols [87]. Polyols are considered as FODMAPs and may have contributed to the reactions caused by these fruits. Galactans are found in food-items such as lentils and are completely malabsorbed in the small intestine, and are most likely to have caused the reactions reported to legumes [87]. It is still uncertain if reduction of FODMAPs alone would have caused the reduction in symptom severities alone in this study.

### *Allergic Hypersensitivity*

Proteins from cow's milk and wheat are common allergens [66]. Some patients in this study reported reactions to dairy products with a lower content of lactose such as fermented milk or white Gouda cheese, thus allergic hypersensitivity to the protein content in these products may be involved. Undiagnosed allergic hypersensitivity to some of the protein compounds found in wheat can also not be excluded.

### *Bioactive Chemicals*

Caffeine beverages, cheeses and fruits contain bioactive chemicals. Caffeine beverages were reported to cause symptoms in 6 of 11 patients during the reintroduction period. Coffee and black tea contain the bioactive chemical salicylates and reactions to this bioactive chemical

cannot be ignored. The patients reported that if they limited their caffeine consumption to approximately two cups of coffee/black tea a day, their symptoms were controlled. This suggests that there may be a 'dose response' to the content in these beverages. Furthermore, these beverages also contain the bioactive chemical, caffeine. Caffeine is known for its stimulatory properties that increase colon activity [112, 113]. The consumption of coffee has also been associated with pain in patients with CD [45]. Hence, it is uncertain if it was the salicylates or caffeine in the caffeine beverages that caused the adverse reactions in this study. Fruits such as apples and pears were found to cause frequent adverse reactions in this study. These fruits are sources of salicylates and this may contribute to the adverse symptoms. As mentioned previously, cow's milk products caused adverse symptoms in this study. Cheese, especially long-ripened cheese like Gouda contains histamines that can cause abdominal pain, abdominal distension and diarrhea [86]. However, if some of the adverse reactions to the intake of fruit, caffeine beverages or cheese found in this study were caused by the chemical contents remain unclear.

#### *Non-celiac Gluten Intolerance*

Wheat products frequently caused adverse reactions in this study. Wheat contains the protein gluten. Some patients in the present study reported that they suspected gluten as a prominent symptom trigger. One study found that in patients where celiac disease was excluded, some patients found that their symptoms still improved on a gluten-free diet [103]. Hence, reactions to gluten in wheat products caused by non-celiac gluten intolerance as proposed by Biesiekierski *et al.* [103], cannot be excluded in the present study. The aetiology behind the proposed non-celiac gluten intolerance is still unknown and relatively unexplored. Notably, one patient in this study had celiac disease and did not include food-items containing gluten. Celiac disease had been excluded in the other patients and hence celiac disease is not discussed.

To summarize, some food groups were found to cause adverse symptoms more frequently than others in the present study. This knowledge may be useful in a clinical setting in the assessment of patients with CD in remission that reports food hypersensitivities. This knowledge may also be useful in the work of developing procedures to identify food symptom triggers. Unfortunately, we did not have the opportunity to conclude what mechanisms that caused the adverse reactions to the food groups found in this study. The symptom responses



to the dietary alteration and the possible underlying mechanisms for these symptoms are discussed henceforth.

### 8.2.2 Immediate vs. Delayed Symptom Responses to the Elimination Diet

The present study aimed to compare the symptom severity of GI symptoms and extraintestinal symptoms from a baseline period where cow's milk and wheat were included to an elimination period where suspected symptom triggers were excluded. It was found that total symptoms as well as the various symptoms significantly decreased from baseline to this elimination period. Furthermore, this study also aimed to compare the symptom severity in GI symptoms and extraintestinal symptoms from the elimination period to the last point of food reintroduction, the endpoint. No significant change was found in symptom severity from the elimination period to this endpoint. This suggests that the patients managed to identify symptoms triggers and find a diet where their symptoms were adequately controlled.

An important finding was that there seemed to be a difference in the time-response to the dietary alteration in the elimination period in the GI symptoms compared to the extraintestinal symptoms. As seen in figure 14 and 15, the symptom severity of fatigue and musculoskeletal pain were lower at the endpoint than during the elimination diet. This suggests that these symptoms may have a delayed response to the elimination diet. This differs from most of the GI symptoms, which seemed to have the lowest frequency of symptom severity during the elimination diet. This may imply that some symptoms need more time for the optimal symptom relief to occur in some patients. Allergic hypersensitivity reactions can be immediate and easy to detect, however it has been implied that allergic reactions may have a more delayed onset, as long as after two weeks after exposure to the food trigger [114]. Hence, if this was the underlying mechanism, it may have been difficult for the patients to identify the food-item(s) responsible for inducing the possible delayed symptom relief. The elimination period of two weeks may have been too short. Gibson and Shepherd [3] proposed that when following the FODMAP strategy, the elimination period should be six to eight weeks to confirm that symptoms are adequately controlled. They advised this because they had experienced that there is an efficacy in symptom response in the first eight weeks following the low FODMAP diet [87].

In the following section, the reported GI symptoms and the extraintestinal symptoms are discussed. The proposed mechanisms behind the adverse reactions to some compounds found in foods are here linked to the symptoms.

### 8.2.3 Possible Mechanisms behind the Gastrointestinal and Extraintestinal Symptoms

Wind, abdominal pain, bloating, odorous wind/feces, diarrhea, fatigue were the most common self-reported symptoms reported at the introduction meeting. This is in consistency with the symptoms recorded throughout the study intervention, except for odorous wind/feces, which was not recorded. These GI symptoms were significantly reduced when the diet was altered. One pilot study indicated that a low FODMAP diet may reduce GI symptoms in patients with CD in remission [19]. Furthermore, most of the patients reported that their GI symptoms became worse throughout the day during the baseline period. They reported that GI symptoms often worsened after a meal, especially regarding bloating. This may correspond with the FODMAP hypothesis. FODMAP is widespread in the Western diet and if the patients frequently ate food-items containing FODMAP, the increased load of FODMAP may produce symptoms due to rapid fermentation and osmotic effect causing increased luminal distension. The symptoms may be less severe in the morning due to overnight fasting and hence no FODMAP exposure. It can also be suggested that this postprandial bloating may be caused by small intestinal bacterial overgrowth, as distension of the small intestine has shown to cause more pain than distension of the colon [92]. Furthermore, symptoms like bloating, abdominal pain and diarrhea have been associated with small intestinal bacterial overgrowth in patients with CD and IBS [40]. The study by Biesiekierski et al. found that abdominal pain increased and that satisfaction with stool consistency decreased in the group exposed to gluten compared to placebo [103]. However the gluten challenge also found that gluten had no significant effect on nausea or wind, suggesting that gluten may affect some GI symptoms more frequently than others [103]. Additionally, GI symptoms can also be caused by sensitivity reactions to bioactive chemicals in some foods, allergic hypersensitivity and subclinical inflammation.

Of the 16 patients at the introduction meeting, 12 and 10 patients reported fatigue and musculoskeletal pain, respectively. These symptoms were significantly reduced when diet was altered. One had Bechterew's disease and reported that his symptoms decreased during

the elimination diet. Several other patients also reported that their fatigue decreased during the elimination diet. One study conducted on IBS-patients found that fatigue increased when they were allocated to a high FODMAP diet [64]. Another study indicated that a low FODMAP diet may reduce fatigue in patients with CD in remission [19]. A controlled study found that fatigue significantly increased when patients with proposed non-celiac gluten intolerance were exposed to gluten compared to placebo [103]. However, the present study provided no clues than can explain why fatigue and musculoskeletal pain appeared to have a delayed time-response compared to the GI symptoms. Expectations of symptom relief or other biases may contribute to the symptom severities reported in this study, however this was beyond our control.

### *Individual Differences*

Importantly, there were individual differences in the symptom responses in this study. For example one patient reported considerably more symptoms and symptom triggers than the other patients. She reported e.g. edema in her legs and hypersensitivity reactions to carbohydrates in her diet. She experienced this as ‘blood sugar falls’. She had excluded many food-items before the study intervention and experienced severe lethargy/fatigue and loss of appetite during the baseline period. Interestingly, her symptoms decreased after week two on the elimination diet and she reported that she now felt ‘hungry again’ and that the edema was gone. Importantly, individual differences like these should be taken into account in clinical practice.

## 9 Conclusion

Patients with CD often experience adverse symptoms related to food intake despite being in remission. Dietary advices and procedures in clinical practice are lacking. Studies have implicated that this patient group has symptoms similar to those in IBS. The present study found that a dietary intervention may reduce both GI symptoms and extraintestinal symptoms in patients with CD in remission that report food hypersensitivities. Importantly, there were individual differences in symptom severity and in the adverse reactions to different food-items. Several mechanisms may cause the food hypersensitivities, however no conclusions of this was made and should be explore further. There were some indications that extraintestinal symptoms and GI symptoms had dissimilar time responses to the elimination diet. Fatigue and musculoskeletal pain had the lowest symptom severity at endpoint, hence the beneficial effects of elimination diets conducted in clinical practice may benefit from expanding the elimination period.

The implication that some CD patients may have food hypersensitivities should be acknowledged and applied to the clinical work of clinical nutritionists and physicians. This knowledge should also be applied to the information material provided by interest organizations.

## 10 Further Research

The implementation and results in this study identified several matters that ought to be investigated further.

One study explored the use of a cytologic assay (basophil activation) in diagnosis of food allergy in patients with IBS [115]. It was found that this test was more sensitive and specific in diagnosing food allergy than the IgE-tests commonly used today [115]. The present study was set out to explore this cytologic assay, but the equipment was not delivered in time for completion of the master thesis. Hence, investigation of this assay as a diagnostic tool to identify allergic hypersensitivity in CD is highly requested. Moreover, improved biomarkers to identify the underlying mechanisms before starting a dietary intervention would be highly beneficial for this patient group, as the procedures used to identify adverse reactions today are often extensive and time consuming. More knowledge about the rather unexplored reactions to bioactive chemicals and the non-celiac gluten intolerance is needed.

The present study excluded both known food triggers in IBS-patients and foods high in FODMAPs during the elimination period. Due to this, controlled studies investigating the efficacy of a low FODMAP diet only, to find if a low FODMAP diet can be used as a dietary intervention in CD patients seem necessary. An analysis of the patients' dietary composition after the study intervention would be useful to find out if the patients end up with an adequate nutritional intake. A follow-up of the patients' symptom severity after six months and one year after the study endpoint is highly requested to evaluate the long term effects of this dietary intervention.

During the recruitment process some patients with ulcerative colitis requested to take part in the study, however they were not included. The study by Gearry *et al.* [19] found that the low FODMAP diet reduced symptoms in patients with ulcerative colitis in remission. Hence, studies of dietary interventions in this patient group are requested.

Further exploration of patients with CD in remission with self-reported hypersensitivities would be highly beneficial for the assessment and development of systematized tools to identify food symptoms triggers in clinical practice.



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## Appendices

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# Appendix 1.

## Approval from the Regional Committee for Research Ethics



<b>Region:</b> REK sør-øst	<b>Saksbehandler: Telefon:</b> Ingrid Middelthun 22845515	<b>Vår dato:</b> 30.06.11	<b>Vår referanse:</b> 2011/1018
		<b>Deres dato:</b>	<b>Deres referanse:</b>

Per Ole Iversen  
Universitetet i Oslo  
Avd. for ernæringsforskning  
0317

### **Diagnose av matallergier hos Morbus Crohn pasienter med selvrapporterte matvarerelaterte symptomer**

Vi viser til svar på merknader av 07.07.11 i forbindelse med komiteens behandling av det ovenfor nevnte forskningsprosjekt.

Prosjektleder er professor dr. med. Per Ole Iversen.

Forskningsansvarlig er Lovisenberg diakonale sykehus ved øverste administrative ledelse.

#### **Vedtak:**

Komiteen har vurdert søknaden og godkjenner prosjektet med hjemmel i helseforskningsloven § 10.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK. Vi gjør oppmerksom på at dersom endringene er vesentlige må prosjektleder sende ny søknad, eller REK kan pålegge at så gjøres.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren», <http://www.norsk-helsenett.no/informasjonssikkerhet/bransjenormen/Personvern%20og%20informasjonssikkerhet%20i%20forskningsprosjekter%20v1.pdf>

Tillatelsen gjelder til 31.12.2012. Av dokumentasjonshensyn skal opplysningene bevares til 31.12.2013. Opplysningene skal lagres aidentifisert i en nøkkel- og en opplysningsfil. De skal deretter anonymiseres eller slettes.

**Postadresse:**  
Postboks 1130 Blindern  
0318 Oslo

**Telefon:** 22845511  
**E-post:** [post@helseforskning.etikkom.no](mailto:post@helseforskning.etikkom.no)  
**Web:** <http://helseforskning.etikkom.no>

Vi ber om at alle henvendelser sendes inn via vår saksportal eller på e-post. Vennligst oppgi vårt referansenummer i korrespondansen.



Prosjektet skal sende sluttmelding til REK Sør-Øst D, se helseforskningsloven § 12, senest 31.06.2013.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-Øst. Klagefristen er tre uker fra mottak av dette brevet.

Med vennlig hilsen

Stein A. Evensen  
professor dr. med.  
leder

Ingrid Middelthon  
seniorrådgiver

---

**Postadresse:**  
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Vi ber om at alle henvendelser sendes inn via vår saksportal eller på e-post. Vennligst oppgi vårt referansenummer i korrespondansen.

## Appendix 2.

Invitation to the introduction meeting

### *Invitasjon til informasjonsmøte*

Vi viser til hyggelig telefonsamtale.

Du er herved invitert til informasjonsmøte om deltagelse i forskningsprosjektet:

#### ***Matvareintoleranser ved Crohns sykdom.***

Håper du har mulighet til å møte opp; det vil bli gitt nyttig informasjon om deltagelse og gjennomføring av prosjektet. Oppmøtet er uforpliktende og du kan når som helst trekke deg.

Følgende temaer vil bli gjennomgått:

- Presentasjon av studien
- Tidslinje for studiedeltagelse
- Gjennomgang av hvilke matvarer man kan spise på eliminasjonsdietten, samt
- Tips og oppskrifter
- Kartlegging av nåværende symptomer ved hjelp av utdelt skjema

Det blir god mulighet til å stille spørsmål.

Vi serverer frukt, kaffe og te.

**Tidspunkt: torsdag 15. September kl. 1600-1800**

**Sted: 2. Etasje, lærings- og mestringssenteret (LMS), Lovisenberg Diakonale**

**Sykehus, Lovisenberggt. 17.** (Spør i resepsjonen i hovedinngangen)

Med vennlig hilsen,

Maren J. Komperød

Masterstudent

Tonje Mellin-Olsen

Klinisk ernæringsfysiolog

Arne Røseth

Gastroenterolog





## Appendix 3. Inquiry to patient/ consent form



**Lovisenberg Diakonale Sykehus**

Forespørsel om deltakelse i forskningsprosjekt

### **Matvareintoleranser ved Crohns sykdom**

#### **Bakgrunn og hensikt**

Dette er et spørsmål til deg om å delta i en forskningsstudie som ønsker å identifisere mulige matvareallergier hos pasienter med Crohns sykdom som er i en god fase av sin sykdom, men som fortsatt har symptomer.

#### **Hva innebærer studien?**

- 1) Blodprøve for å teste matvareallergi. Mål av høyde og vekt.
- 2) Utredning av matvareintoleranse ved eliminasjonsdiett (streng diett der matvarer som er kjent for å gi symptomer utelates) og senere reintroduksjon av en og en matvare:
  - Informasjonsmøte om studien med gjennomgang av diettene. Symptomer vil også kartlegges.
  - Vanlig kost i 2 uker. Mat og symptomdagbok skal fylles ut.
  - Eliminasjonsdiett i 2 uker. Mat og symptomdagbok skal fylles ut.
  - Reintroduksjon av matvarer i 4-8 uker. Mat og symptomdagbok skal fylles ut.

#### **Mer detaljert beskrivelse finnes i vedlagte infobrosjyre.**

- 3) Innsyn i pasientjournalen for å finne opplysninger om diagnose og behandling av Crohns sykdom fra legenotater og blodprøvesvar.

Studiedeltager forventes å møte opp til avtaler og følge avtalt opplegg for eliminasjonsdiett og gjeninnføring av matvarer.

Tidsskjema: Deltageren inkluderes av lege i perioden juli-august 2011. Deltagelsen i prosjektet varer fra august 2011 til maksimalt desember 2011.

#### **Mulige fordeler og ulemper**

Fordelen er at du vil få hjelp til å identifisere matvarer du reagerer på og få hjelp til å finne et kosthold der du får mindre mage- tarmproblemer. På sikt vil erfaringene fra studien også kunne hjelpe andre med samme diagnose. Ulempene er at det er tidkrevende og sosialt utfordrende å følge en eliminasjons- og provokasjonsdiett.

#### **Hva skjer med prøvene og informasjonen om deg?**

Prøvene og informasjonen som registreres om deg, skal kun brukes slik som beskrevet i hensikten med studien. Resultatene vil også finnes i pasientjournalen og være grunnlag for videre behandling. 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. Blodprøvene vil bli analysert omgående etter de er tatt og kastet etter analysering.

Det er kun veiledere og student knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Resultatene vil publiseres anonymt i en masteroppgave og i et fagtidsskrift slik at identiteten til deltagerne ikke kommer frem.

Dataene lagres i 5 år på sykehusets forskningsserver, slik kravet er for forskningsstudier. Alle resultater dokumenteres også i sykehusjournalen din.

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 prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Deltagerne har rett til informasjon om utfallet av studien først når studien er avsluttet.

#### **Frivillig deltakelse**

Det er frivillig å delta i studien. Du kan når som helst, og uten å oppgi noen grunn, trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på denne siden. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling.

#### **Aktuelle telefonnumre:**

Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte masterstudent i klinisk ernæring Maren Komperød tlf. 95456410 eller klinisk ernæringsfysiolog Torunn Knudsen tlf. 23226392.

## **Samtykke til deltakelse i studien**

Jeg har fått utlevert og lest deltagerinformasjon og har fått muntlig informasjon om studien.

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

Jeg er villig til å delta i studien



-----  
(Prosjektdeltaker, dato)



Jeg bekrefter å ha gitt informasjon om studien


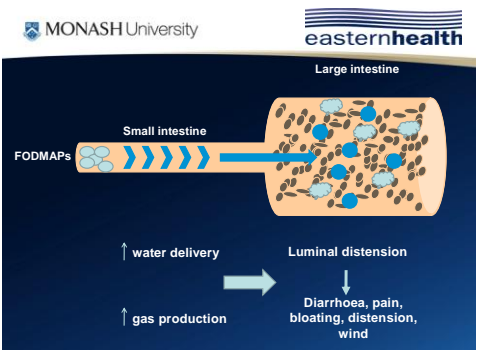
-----  
(Ansvarlig lege, dato)

## Appendix 4.

Power point slides presented to the patients at the introduction meeting

	<p>Matvareintoleranser ved Crohns sykdom</p> <p>Masteroppgave i klinisk ernæring Maren J Komperød 2011/2012</p>	 <p><i>Hva skjer i dag?</i></p> <ul style="list-style-type: none"> <li>• Litt om bakgrunn for studien</li> <li>• Tidslinje for studiedeltagelse</li> <li>• Helhetlig gjennomgang av skjemaer som skal fylles ut</li> <li>• Symptomkartlegging</li> <li>• Eliminasjonsdietten, tips og oppskrifter</li> <li>• Samtykkeskjema</li> <li>• Mål av høyde og vekt (privat på eget rom)</li> </ul>
---	---	--

 <p><i>Bakgrunn for studien</i></p> <p>Pasienter med Crohns i en god fase av sin sykdom opplever ofte symptomer knyttet til matinntak.</p> <p>Hva kan være grunnen?</p>	 <p><i>Bakgrunn for studien</i></p> <p>Allergi ?</p> <p>Svekket/nedsett barrierefunksjon på tarmmucosa →</p> <p>Økt opptak av ufordøyde proteiner i blodbanen →</p> <p>Trigger immunsystemet → Utvikling av allergi</p> <p style="text-align: right;"><small>Ref: Bichhoff &amp; Crowe, 2005</small></p>
---	--

 <p><i>Bakgrunn for studien</i></p> <p>Overfølsomhet for FODMAPs ? (Fermentable Oligo-, Di-, and Monosaccharides and Polyols)</p> <p>Små molekyler som er lett fermenterbare.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2">De vanligste FODMAPs i norsk kosthold</th> </tr> <tr> <th>FODMAPs</th> <th>Matvarer</th> </tr> </thead> <tbody> <tr> <td>Fruktose</td> <td>Epler, pærer, vannmelon, asparges, honning</td> </tr> <tr> <td>Laktose</td> <td>Kumelk, youghurt, ost</td> </tr> <tr> <td>Sukkeralkoholer</td> <td>Epler, nektariner, pærer, tyggis og drikker med kunstig søtning, blomkål</td> </tr> <tr> <td>Fruktaner</td> <td>Linsler og bønner, rug, hveite, pistasjnøtter</td> </tr> </tbody> </table>	De vanligste FODMAPs i norsk kosthold		FODMAPs	Matvarer	Fruktose	Epler, pærer, vannmelon, asparges, honning	Laktose	Kumelk, youghurt, ost	Sukkeralkoholer	Epler, nektariner, pærer, tyggis og drikker med kunstig søtning, blomkål	Fruktaner	Linsler og bønner, rug, hveite, pistasjnøtter	 <p style="text-align: center;">MONASH University <span style="float: right;">easternhealth</span></p> <p style="text-align: center;">Small intestine → Large intestine</p> <p style="text-align: center;">FODMAPs → ↑ water delivery → Luminal distension → Diarrhoea, pain, bloating, distension, wind</p> <p style="text-align: center;">↑ gas production</p>
De vanligste FODMAPs i norsk kosthold													
FODMAPs	Matvarer												
Fruktose	Epler, pærer, vannmelon, asparges, honning												
Laktose	Kumelk, youghurt, ost												
Sukkeralkoholer	Epler, nektariner, pærer, tyggis og drikker med kunstig søtning, blomkål												
Fruktaner	Linsler og bønner, rug, hveite, pistasjnøtter												



### Bakgrunn for studien

Pasienter med Crohns i en god fase av sin sykdom opplever ofte symptomer knyttet til matinntak.

Hva kan være grunnen?

Allergi, FODMAPs eller begge deler?

### Tidslinje for deltagelse i studien

Informate	1	2	3	4	5	6	7	8	9	10	11	12
Symptom kartlegging	Vanlig kost		Eliminasjonsdiett		Reintroduksjon av matvarer							
Samtykkeskjema	Utfylling av mat og symptom dagbok		Utfylling av mat og symptom dagbok		Utfylling av mat og symptom dagbok							
Høyde, vekt	VAS		VAS		VAS							

Maria J. Korpstad



### Symptomkartlegging

Kartlegging av matvarer dere opplever å reagere på

Brukes som hjelpemiddel for gjeninnføringsperioden

Skal bare fylles inn idag

Lovisenberg Diakonale Sykehus  
Maria J. Korpstad 07.08.17



### VAS (visual analogue scale) og symptomregistrering

Begge to skal fylles ut hver dag gjennom hele perioden

VAS er hoveddatamateriale

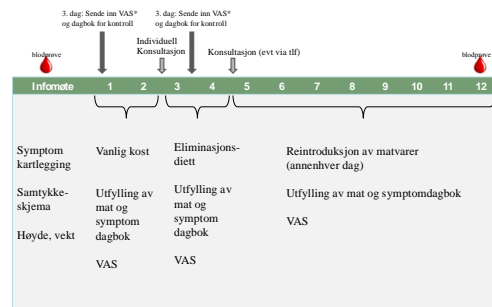
Symptomskjema brukes som hjelpemiddel for gjeninnføring av matvarer



### Blodprøver

En generell blodprøve tas ved sykehuset før eliminasjonsdietten (du får rekvisisjon til å ta blodprøver av ?)

Etter gjeninnføringsperioden skal vi ta en blodprøve for å se om du har en allergi som de matvarene du er overfølsom for



VAS\*, Visual Analogue Scale

# Symptomkartlegging

Kartlegging av matvarer dere opplever å reagere på

Brukes som hjelpemiddel for gjeninnføringsperioden



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## Symptomkartlegging

Kode nr. \_\_\_\_ Dato \_\_\_\_

1: Ring rundt de symptomene du opplever av de som er gjengitt nedenfor.

Mage- tarmsymptomer	Andre fysiske symptomer	Psysiske symptomer
1. Brekninger	8. Hovne lepper	16. Dølig humør
2. Oppblåsthet	9. Utdelt/ rødhet	17. Konsentrasjonsvansker
3. Luffavgang	10. Andre levelever	18. Umatte
4. Vond lukt av avføring/luffavgang	11. Hjerterbank	
5. Magesmerter	12. Pustevansker	
6. Diaré	13. Kløe	
7. Forstoppelse	14. Hodepine/ migrene	
	15. Muskel/ leddmerter	

2: På de 4 neste sidene skal du fylle ut informasjon om ulike matvarer. Bruk tallene ovenfor for å beskrive symptomene. Fyll også en hvor lenge symptomene varer (varighet). Hvor lang tid det tar før symptomene inntrer/ etter inntak av en bestemt matvare (debut) og opplevd intensitet (symptomintensitet) av symptomet beskrevet med tallene 1,2,3 og 4, der: 1= svak, 2= moderat, 3= sterk og 4= meget sterk.

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Matvare	Spiser matvaren?		Hvis NEI på forrige: Hvorfor ikke?		Symptomer (ang gi alle fra forrige side)	Debut (hvor lang tid etter inntak)	Varighet (hvor lenge)	Intensitet (ang 1,2,3,4)
	JÅ	NEI	Tåler ikke	Liker ikke				
Eple								
Pære								
Appelsin								
Saksebrøder								
Vanemelk								
Honnig								
Tørket frukt								
Alpargos								
Hermelinst frukt								
Brunost								
Korv								
Yoghurt								
Ost								
Varifossas								
Fløst								
Amme								
Spinnaker								
Nakstener								
Plommer								
Eplepære juice								
Sukkerfyllt eggagurk eller drøps								
Avokado								

# Matvarer og tipstil eliminasjonsdietten





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### Eliminasjonsdietten

Eliminasjon av matvarer som er kjent for å gi ubehag, være vanskelig, frukt og grønnsaker som kan skape tarmsymptomer (såkalt FODMAP\*\*)


Du kan spise følgende matvarer:

<p><b>Cerealier</b></p> <ul style="list-style-type: none"> <li>Bokhvete</li> <li>Hirse</li> <li>Puffet ris</li> <li>Quinoa</li> <li>Ris</li> <li>Risikaker</li> <li>Risnudler</li> </ul> <p><b>Kjøtt og fisk</b></p> <ul style="list-style-type: none"> <li>Bacon</li> <li>Fisk, alle typer*</li> <li>Kalkun</li> <li>Kylling</li> <li>Skildpadde</li> <li>Skjole</li> <li>Svinesteg</li> <li>Tofu</li> <li>Tunfisk på boks i vann</li> <li>Viltkjøtt</li> </ul> <p>* Unntatt ved kjent allergi</p>	<p><b>Melkestatninger</b></p> <ul style="list-style-type: none"> <li>Rømme</li> <li>Soyamelk</li> </ul> <p><b>Grønnsaker</b></p> <ul style="list-style-type: none"> <li>Agurk</li> <li>Aubergine</li> <li>Blåbær</li> <li>Brokkoli (&lt; 1 di/dag)</li> <li>Ener (&lt; 0,5di/dag)</li> <li>Fennikel (&lt; 1 di/dag)</li> <li>Gulrot</li> <li>Ingeliser</li> <li>Kiniskål og annen kål</li> <li>Kålrot</li> <li>Nepi</li> <li>Pastinak</li> <li>Rødrot</li> <li>Rosekål (&lt; 1 di/dag)</li> <li>Selleri</li> <li>Spirat</li> <li>Squash</li> <li>Svampet (&lt; 1di/dag)</li> <li>Vårhak (den grønne delen)</li> </ul>	<p><b>Frukt og bær</b></p> <ul style="list-style-type: none"> <li>Ananas</li> <li>Avokado (en kvart/dag)</li> <li>Banan</li> <li>Blåbær</li> <li>Bringebær</li> <li>Centaloupemelon</li> <li>Druer</li> <li>Honningsmelon</li> <li>Jambuer</li> <li>Kori</li> <li>Papayefrukt</li> <li>Rabarber</li> <li>Sjemeffrukt</li> </ul> <p><b>Friske Urter</b></p> <ul style="list-style-type: none"> <li>Basilikum</li> <li>Cresskik</li> <li>Koriander</li> <li>Pepper</li> <li>Rosmarin</li> <li>Timian</li> </ul> <p><b>Andre Krydder</b></p> <ul style="list-style-type: none"> <li>Chili</li> <li>Pepper</li> <li>Salt</li> <li>Sukker (begrenset)</li> <li>Tamar soyasaus</li> </ul> <p><b>Fetskilder</b></p> <ul style="list-style-type: none"> <li>Oliveneje</li> <li>Rapsolje</li> </ul>	<p><b>Drømme</b></p> <ul style="list-style-type: none"> <li>Ren urtete</li> <li>Oppkokt vann eller vann på flaske uten kullsyre</li> </ul> <p><b>Annet</b></p> <ul style="list-style-type: none"> <li>Bakpulver</li> <li>Olivener</li> <li>Sotsikkejernte (i &lt;2ss/dag)</li> </ul> <p>** Kilde: The low FODMAP Diet, reducing poorly absorbed intestinal symptoms, Eastern Health Clinical School, Monash University, 2010.</p>
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Manns J Kongsrud 05.08.11

# Samtykkeskjema



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## Appendix 5.

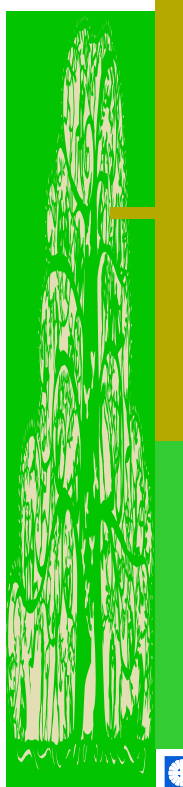
Leaflet with information about the study procedure and the elimination diet



### Slik går vi fram:

- 1) **Introduksjonsmøte** for alle som er med i studien.  
Tema: Generell informasjon og gjennomgang av eliminasjonsdietten og fremgangsmåte for gjeninnføring av matvarer. Deltagerne fyller ut kartleggingsskjema for symptomer.
- 2) **Vanlig kost i 2 uker**, der du i størst mulig grad inkluderer matvarer du mener du reagerer på. Mat- og symptomdagbok skal fylles ut. Hensikten er å kartlegge omfanget av symptomer.
- 3) **Eliminasjonsdiett i 2 uker**, der du kun spiser matvarene i denne brosjyren. Du vil bli gitt menyeksempler og individuell oppfølging. Mat- og symptomdagbok skal fylles ut. Målet er symptomfrihet.
- 4) **Reintroduksjon i 4-8 uker**, der matvarer gjeninnføres annenhver dag. Individuell oppfølging. Mat- og symptomdagbok skal fylles ut. Hvis du får tilbakefall av symptomer, kutter du ut den sist innførte matvaren. Når du igjen blir symptomfri, kan du fortsette å teste ut nye matvarer. Målet er å finne ut hvilke matvarer du trygt kan spise uten å få mage-tarmplager.

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### Informasjon om eliminasjonsdiett og gjeninnføring av matvarer

For deg som har Crohns sykdom og mage-tarmplager



Utredning av matvareintoleranse ved masterstudent i klinisk ernæring, Maren Komperød, i samarbeid med Enhet for klinisk ernæring og Unger Vetlesens Institutt

Aug 2011

### Eliminasjonsdietten

Eliminasjon av matvarer som er kjent for å gi allergi, samt cerealier, frukt og grønnsaker som kan skape tarmproblemer (såkalt FODMAP\*\*)



Du kan spise følgende matvarer:

#### Cerealier

Bokhvete  
Hirse  
Puffet ris  
Quinoa  
Ris  
Riskaker  
Risnudler

#### Kjøtt og fisk

Bacon  
Fisk, alle typer\*  
Kalkun  
Kylling  
Skalldyr\*  
Skinke  
Svinekjøtt  
Tofu  
Tunfisk på boks i vann  
Viltkjøtt

\* Utelates ved kjent allergi

#### Melkeerstatninger

Rismelk  
Soyamelk

#### Grønnsaker

Agurk  
Aubergine  
Bladsalat  
Brokkoli (< 1 dl/dag)  
Erter (< 0.5dl/dag)  
Fenikkel (< 1 dl/dag)  
Gulrot  
Ingefær  
Kinakål og annen kål  
Kålrot  
Nepe  
Pastinakk  
Rødbet  
Roselkål (< 1 dl/dag)  
Selleri  
Spinat  
Squash  
Søtpotet (< 1dl/dag)  
Vårløk (den grønne delen)

#### Frukt og bær

Ananas  
Avokado (en kvart/dag)  
Banan  
Blåbær  
Bringebær  
Cantaloupemelon  
Druer  
Honingmelon  
Jordbær  
Kiwi  
Pasjonsfrukt  
Rabarbra  
Stjernefrukt

#### Friske Urter

Basilikum  
Gressløk  
Koriander  
Persille  
Rosmarin  
Timian

#### Andre Krydder

Chili  
Pepper  
Salt  
Sukker (begrenset)  
Tamari soyasaus

#### Fettkilder

Olivenolje  
Rapsolje

#### Drikke

Ren urtete  
Oppkokt vann  
eller vann på flaske  
uten kullsyre

#### Annet

Bakepulver  
Oliven  
Solsikkekjerner/frø (<2ss/dag)



\*\* Kilde ; *The low FODMAP Diet, reducing poorly absorbed Sugars to control gastro-Intestinal symptoms*, Eastern Health Clinical School, Monash University, 2010.





## Appendix 6.

Leaflet with suggestions for recipes and food choices during the elimination period.

Prepared by the author.

**TIPS**

Olivenolje med smak:

Skjær hvitløk eller chili i biter. Bland bitene sammen med olivenolje på en flaske i ca 1 uke.


Bruk til mild steking, til ovnsbaking eller over grønnsaker.

*Pass på at du ikke spiser bitene med hvitløk- bare oljen!*

**Internett:**

Det finnes mye inspirasjon på internett. Men husk å bare spise det som står på listen i denne brosjyren.

Laget av Maren J Komperød, masterstudent klinisk ernæring, 2011

 Lovisenberg Diakonale Sykehus

**Oppskrifter og tips**



For deg som har Crohns sykdom og mage-tarmplager

Laget av Maren J Komperød, masterstudent klinisk ernæring, 2011

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### SØTT OG GODT

#### MUFFINS

Ca 6 muffinsformer

Bland sammen i en bolle:

- 80 g bokhvitemel
- 1 ts bakepulver
- 40 g sukker
- 0.7 dl soyamelk
- 6 jordbær i små biter (kan bruke blåbær, banan eller bringebær).
- 30 g rapsolje
- 3 mynteblader (valgfritt)

Stek på 200grader i ca 20 minutter.



#### SMOOTHIE

Ca 2 porsjoner

- 1 banan
- 2 dl jordbær eller blåbær
- 1 dl soyamelk

Del opp banen og ha alt i en blender eller mos med stavmikser.

Ananas og kiwi er også godt sammen, eller hver for seg i smoothie. Ha i kiwi tilslutt, så ikke steinene blir most i blender.



### MIDDAGSFORSLAG

#### VEGGISWOK

4 pers

1. Kutt opp 1 vårløk, 4 buketter brokkoli, 4 gulrotter, 2 pastinakk, litt revet ingefær, og 1 squash.
2. wok på høy varme med rapsolje.
3. Stek ca 300 g tofubiter. Krydre med tamari, pepper og hvitløksolje.
4. Kok 200 g risnudler i 2min. (Kan bruke ris eller quinoa).
5. Bland alt sammen sammen når nudlene er ferdig. Krydre med f eks tamari, pepper, chili, koriander.

#### KYLLING OG ROT

4 pers

1. Kutt opp 1 stor søtpotet, 4 gulrotter og 2 pastinakk.
2. Legg i ovnsfast form, hell over olivenolje, fersk basilikum, salt og pepper.
3. Stek i ovnen på 200 grader ca 30. minutter.
4. Mens grønnsakene står i ovnen: stek 4 kyllingfileter i rapsolje. Krydre med salt og pepper.
5. Kok opp quinoa eller ris.

Mer saus eller smak? Olivenolje eller tamari soyasaus.



Tamari soya saus

## MIDDAGSFORSLAG

## LAM &amp; ROTSTAPPE

4 pers

1. Mariner 4-6 lammekoteletter eller skiver av lammelår med hvitløksolje, urter, salt og pepper.

3. Rotstappe:  
Kok møre 1 søtpotet, 1 kålrot og 6 gulrøtter.

2. Ha 1 ss olivenolje, 2 ss soyamelk over rotfruktene og mos sammen til en stappe.

4. Stek kjøttet i panne eller på grill og server med rotstappe!

Krydre med salt, pepper og urter etter smak.

## PASTA &amp; TUNFISKSALAT

4 pers

Du trenger:  
1 boks tunfisk i vann  
1 vårløk  
Bladsalat etter ønske  
2 dl spinat  
½ agurk  
1 avokado

1. Kok 150-200gram bokhvete pasta (følg anvisning på pakken).

2. Del opp grønnsakene og bland alt sammen i en stor bolle sammen med den ferdige pastaen og tunfiskene.

Krydre med koriander, litt hvitløksolje, pepper og evt chili.

## FROKOST &amp; LUNSJ

## BOKHVETEGRØT\*

1 dl knust bokhvete  
2 dl kokende vann (tømmes av)  
3 dl vann/soya/rismelk  
1 ts salt

1. Det kokende vannet slås først over grynene, og helles av med en gang.

2. Så koker man gryn, og vann/melkblendingen i ca 5 minutter.

3. Spises med tilbehør som vanlig havregrynsgrot (bær, sukker, banan..)

## Mellommåltid/ kvelds lunsj

Forslag:

1 gulrot, oppskåret frukt, noen oliven eller bær (evt m/ris/soyamelk)

Hjemmelaget Smoothie

Riskake med most avokado og salt og pepper.

Hjemmelaget muesli

Hjemmelagde knekkebrød

**Tips: Lag store middagspor sjoner og ta med restene til lunsj!**

\*(kilde: allergikokken.no)

## FROKOST OG LUNSJ

## PUFFET RIS

med for eksempel ris/soyamelk, banan, jordbær, blåbær eller bringebær

## MUESLI

2 ss rapsolje  
2 ss sukker  
200 g bokhvete flak  
150 g quinoa flak  
100 g hirse flak  
1 ts malt ingefær  
1 ts salt

Varm sammen ingrediensene i en kjele og fordel på et stekebrett.

Brunes på varmluft i ca 20 min (Pass på, blir fort brent!)

Spises med ris/soyamelk, frukt Og/eller bær over.

## KNEKKEBRØD

Sett ovnen på 150 grader

Bland sammen i en bolle:  
70 g bokhvete flak (flingor)  
100 g quinoa flak  
30 g solsikkekjerner  
60 g bokhvete mel  
Ca 4dl vann  
½ ts sukker  
1 ts salt  
2 ts rapsolje

1. Smør blandingen så tynt som mulig ut på 2 stekebrett. Bruk pizzaskjærer til å dele opp til passe store knekkebrød.

2. Sett i ovnen ca 20 minutter. Bytt så plass på brettene. Stek 20 minutter til.

3. Stek så med ovnen på gløtt i 20-30 minutter. Ferdig når gyllenbrune og sprø.

Kan spises som de er eller med avokado, jordbær eller rent kjøtt i tynne skiver.

## FROKOST OG LUNSJ

## PUFFET RIS

med for eksempel ris/soyamelk, banan, jordbær, blåbær eller bringebær

## MUESLI

2 ss rapsolje  
2 ss sukker  
200 g bokhvete flak  
150 g quinoa flak  
100 g hirse flak  
1 ts malt ingefær  
1 ts salt

Varm sammen ingrediensene i en kjele og fordel på et stekebrett.

Brunes på varmluft i ca 20 min (Pass på, blir fort brent!)

Spises med ris/soyamelk, frukt Og/eller bær over.

## KNEKKEBRØD

Sett ovnen på 150 grader

Bland sammen i en bolle:  
70 g bokhvete flak (flingor)  
100 g quinoa flak  
30 g solsikkekjerner  
60 g bokhvete mel  
Ca 4dl vann  
½ ts sukker  
1 ts salt  
2 ts rapsolje

1. Smør blandingen så tynt som mulig ut på 2 stekebrett. Bruk pizzaskjærer til å dele opp til passe store knekkebrød.

2. Sett i ovnen ca 20 minutter. Bytt så plass på brettene. Stek 20 minutter til.

3. Stek så med ovnen på gløtt i 20-30 minutter. Ferdig når gyllenbrune og sprø.

Kan spises som de er eller med avokado, jordbær eller rent kjøtt i tynne skiver.

# Appendix 7.

## Food- and symptom recall



### Symptomregistrering

SYMPTOMER - angi aktuelle siffer som gjengitt nedenfor

Dato:

Navn:

Fødselsdato:

#### Mage- tarmsymptomer

1. Brekninger
2. Oppblåsthet
3. Hyppig luftavgang
4. Vond lukt av avføring/luftavgang
5. Magesmerter
6. Diaré
7. Forstoppelse

#### Andre fysiske symptomer

8. Hovne lepper
9. Utslett/ rødhet
10. Andre hevelser
11. Hjertebank
12. Pustevansker
13. Kløe
14. Hodepine eller migrene
15. Muskel eller leddsmerter

#### Psykiske symptomer

16. Dårlig humør
17. Konsentrasjonsvansker
18. Utmattelse

Debut: Angi når symptomet inntreffer etter matinntak av matvaren som er presisert i skjema(min/timer)

Varighet: Angi varigheten av symptomet (min/timer/dager)

Symptomintensitet: Angi opplevd intensitet av symptomet ved å bruke disse sifferne:

- 1- svak
- 2-moderat
- 3-sterk
- 4-meget sterk



Matvare	Spises matvaren?		Tåler ikke/ Liker ikke	Symptomer (angi siffer)	Debut	Varighet	Symptomintensitet (angi 1, 2, 3 eller 4)
	JA	NEI					
KIWI							
EPLER							
PÆRE							
BANAN							
APPELSIN							
VANNMELON							
ANDRE							
TOMAT							
GULROT-RÅ							
ERTER							
KÅL							
LØK							
HVITLØK							
POTET							
ANDRE							



## Appendix 8.

## Visual analogue scale

**Skala over daglige symptomer**

**Denne dagboken skal fylles ut hver dag gjennom hele studien**

uke \_\_\_\_\_ Dag \_\_\_\_\_ Kode nr \_\_\_\_\_ Dato \_\_\_\_\_

Periode: Vanlig kost  Eliminerasjonsdiett  Reintroduksjon

Har du hatt symptomer i dag?

Ikke i det hele tatt \_\_\_\_\_ 10cm \_\_\_\_\_ Maksimalt

Har du hatt magesmerter i dag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

Har du vært oppblåst i dag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

Har du hatt avvikende avføring i dag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

Har du hatt luftavgang i dag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

Har du vært utmattet i dag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt


Har du hatt ledd-og/ eller muskelsmerter idag?

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

Annet symptom\*.....

Ikke i det hele tatt \_\_\_\_\_ Maksimalt

\*Her kan du fylle inn symptom som ikke er på dette skjemaet, men som vi har blitt enige om å ta med.

 **Lovisenberg Diakonale Sykehus**

Maren J Komperød 08.09.11



## Appendix 9.

Food- and symptom diary

### Mat- og symptomregistrering

Uke nr \_\_\_\_ Periode \_\_\_\_\_ Kode \_\_\_\_\_

Symptom **1**:Magesmerter, **2**:Oppblåsthet, **3**: Avvikende avføring **4**:Luftavgang, **5**:Utmattelse,

**6**:Ledd -/muskelsmerter

Registrer (sett in tall) tidspunkt du eventuelt opplever de symptomene som er nevnt ovenfor, i skjemaet,

**sett ring rundt tallet hvis symptomet er ekstra ille.**

	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Mat spist i tidsrommet:  <b>2400-1000</b>							
Symptom							
Mat spist i tidsrommet:  <b>1000-1500</b>							
Symptom							
Mat spist i tidsrommet:  <b>1500-1900</b>							
Symptom							
Mat spist i tidsrommet:  <b>1900-2400</b>							
Symptom							





## Appendix 10.

Table 11. Modified exclusion diet for IBS, by Parker *et al.* (1995)

<b>Foods not allowed</b>	<b>Foods allowed</b>
Beef	All other types of meat
Fish in batter or breadcrumbs	White/oily/tinned fish in brine/oils
Potatoes, onions, sweet corn, Tinned vegetables,	All other vegetables, fresh/frozen/tinned
Citrus fruits	All other fruits, fresh/frozen/tinned
Wheat, rye, barley, corn	Rice, arrowroot, tapioca, sago, millet, buckwheat, soya flour
Dairy products, sheep/goat's milk, eggs	Soy milk, milk-free margarine
Tea, coffee, alcohol, citrus fruit juice/squash, tap water	Herbal tea, other fruit juice, blackcurrant squash, mineral water
Yeast, gravy mixes, marmalade, salad cream/dressing, blended oils, corn oils	Salt, herbs, spices, honey, syrup, sugar gravy browning (caramel and salt only)
Vinegar, nuts, chocolate	Dried fruit/seeds, carob



## Appendix 11.

Table 12. The low FODMAP guide prepared at Eastern Health Clinical School and published by Monash University, 2010

<i>Vegetables</i>	<i>Fruits*</i>	<i>Bread and cereals</i>	<i>Nuts and herbs</i>
Alfalfa	Avocado (<1/4)	Biscuits, gluten and fruit free	Pine nuts (1Tb)
Bamboo shoots	Banana	Bread, gluten free	Pumpkin seeds (1 Tb)
Beans, green	Blueberry	Bread, spelt	Sunflower seeds (2 tsp)
Bean sprouts	Cantaloupe	Cornflakes	Basil
Bok choy	Carambola	Muesli (wheat free, fruit free)	Coriander
Broccoli (<1/2 cup)	Durian	Oats	Parsley
Brussel sprouts (<1/2 cup)	Grapefruit	Oat bran	Rosemary
Capsicum	Grapes	Pasta, gluten-free	Thyme
Carrot	Honeydew melon	Quinoa	
Celery (1 stick)	Kiwifruit	Rice	
Chives	Lemon	Rice bran	
Choko	Lime	Rice-based crackers	
Choy sum	Longon (<10)	Rice cereals	
Corn (<1/2 cob)	Lychee (<5)	Rice noodles	
Cucumber	Mandarin		
Eggplant	Orange		
Endive	Paw paw	<i>Milk products**</i>	<i>Protein sources</i>
Fennel (<1/2 cup)	Passionfruit	Cheese, hard	Meat
Ginger	Pineapple	Cheese, soft in small amounts	Chicken
Lettuce	Rambutan (<3)	Milk, lactose free	Fish
Olives	Raspberry	Rice milk	Egg
Parsnip	Rhubarb	Yoghurt, lactose-free	Tofu
Peas (<1/4 cup)	Strawberry	Yoghurt, regular, in small amounts	
Poatato	Tangelo		
Pumpin, butternut (1/2 cup)			
Silverbeet			
Spinach			
Sping onion (green part)			
Swede			
Sweet potato (<1/2 cup)			
Turnip			
Zucchini			

\*Relevant if fructose malabsorption, limit to one serving per sitting. \*\*Relevant if lactose intolerant



## Appendix 12.

Sample of one patient's reintroduction period

UKE 5	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare		Sort te		Potet, kokt.		Gulrot		Egg

UKE 6	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare			Tomat		Sopp		Løk	

UKE 7	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare		Blomkål Sukkererter		Kikerter Linser		Honning Rosiner		Russisk salat

UKE 8	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare			Baconost		Brød (en type)		Digestive- kjeks	

UKE 9	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare		Saltstenger		Knekkebrød (en type)		Soyasaus, vanlig.		Hvetebolle

UKE 10	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare			Pasta av durum hvete		Sjokoladekjeks		Kaffe	

UKE 11	Dag	Mandag	Tirsdag	Onsdag	Torsdag	Fredag	Lørdag	Søndag
Matvare			Kaffe med melkepulver		Vaniljesaus		Kumelk	



## Appendix 13

Table 12. Values from the routine medical test from patients who completed the study intervention

Biomarkers	Patient number											
	1	2	3	4	5	6	7	8	9	10	11	12
Hemoglobin (M:13.4-17.0, F: 11.7- 15.3 g/ dl)	13.9	14.5	15.2	14.2	14.5	6.7	15.2	14.4	12.9	14.5	14.6	12.9
MCV (82- 98 fl)	89	MV	87	93	87	<b>103</b>	MV	91	95	88	95	93
Ferritin (10-200 µg/l)	32	51	184	48	150	<b>300</b>	33	50	MV	MV	MV	MV
Vitamin B <sub>12</sub> (140-600 pmol/l)	200	263	<b>1153</b>	<b>671</b>	191	200	505	464	MV	MV	MV	MV
Folate (> 8 nmol/l)	18.5	18.2	15.3	42.9	15.7	11.5	11.2	22.4	MV	MV	MV	MV
Thrombocytes (145-390 10 <sup>9</sup> /l)	275	MV	361	295	216	235	MV	282	327	296	255	249
CRP (0-10 mg/l)	5	2	1	1	4	4	1	2	5	5	<1	<1
White blood cells (3.5-10 10 <sup>9</sup> /l)	7.4	8.1	9.9	5.4	5.1	3	5.2	5.4	6.2	<b>11.1</b>	5.4	6.3
Potassium (3.5-4.4 mmol/l)	4.3	4.4	4.0	4.4	4.2	4.4	4.3	4.4	4.4	4.3	4.2	3.9
Sodium (137-145 mmol/l)	144	141	142	143	143	142	141	141	137	142	141	141
Creatinine (50-90 µmol/l)	MV	67	71	78	89	MV	71	59	MV	86	58	61
Glucose (4-6 mmol/ l)	4.8	MV	5.3	4.1	4.9	4.9	5.2	6.1	5.7	4.5	4.2	5.1
ALAT (M:10-70, F:15-45 U/l)	19	18	20	19	16	9	31	29	46	23	15	11
Urea (F: 2.6-6.4, M: 3.2-8.1 mmol/l)	3	MV	3.7	7.2	3.6	4.4	MV	3.8	MV	MV	3.8	4.5
Calcium* (2.15-2.55 mmol/l)	2.25	MV	2.32	2.19	2.23	2.14	MV	2.26	2.49	2.20	2.20	2.35
Albumin (36-48 g/l)	45	<b>49</b>	<b>50</b>	<b>51</b>	46	47	MV	<b>49</b>	43	42	<b>49</b>	47

Note: P. no, patient number. M, male; F, female; MVC, mean erythrocyte count. Reference values are given in parentheses. Values deviant from the reference values are shown in bold. MV, missing biomarker value from this patient; \*Albumin adjusted calcium





## Appendix 14.

Overview of all food-items stated and number of patients reporting a reaction. Results from the food- and symptom recall.

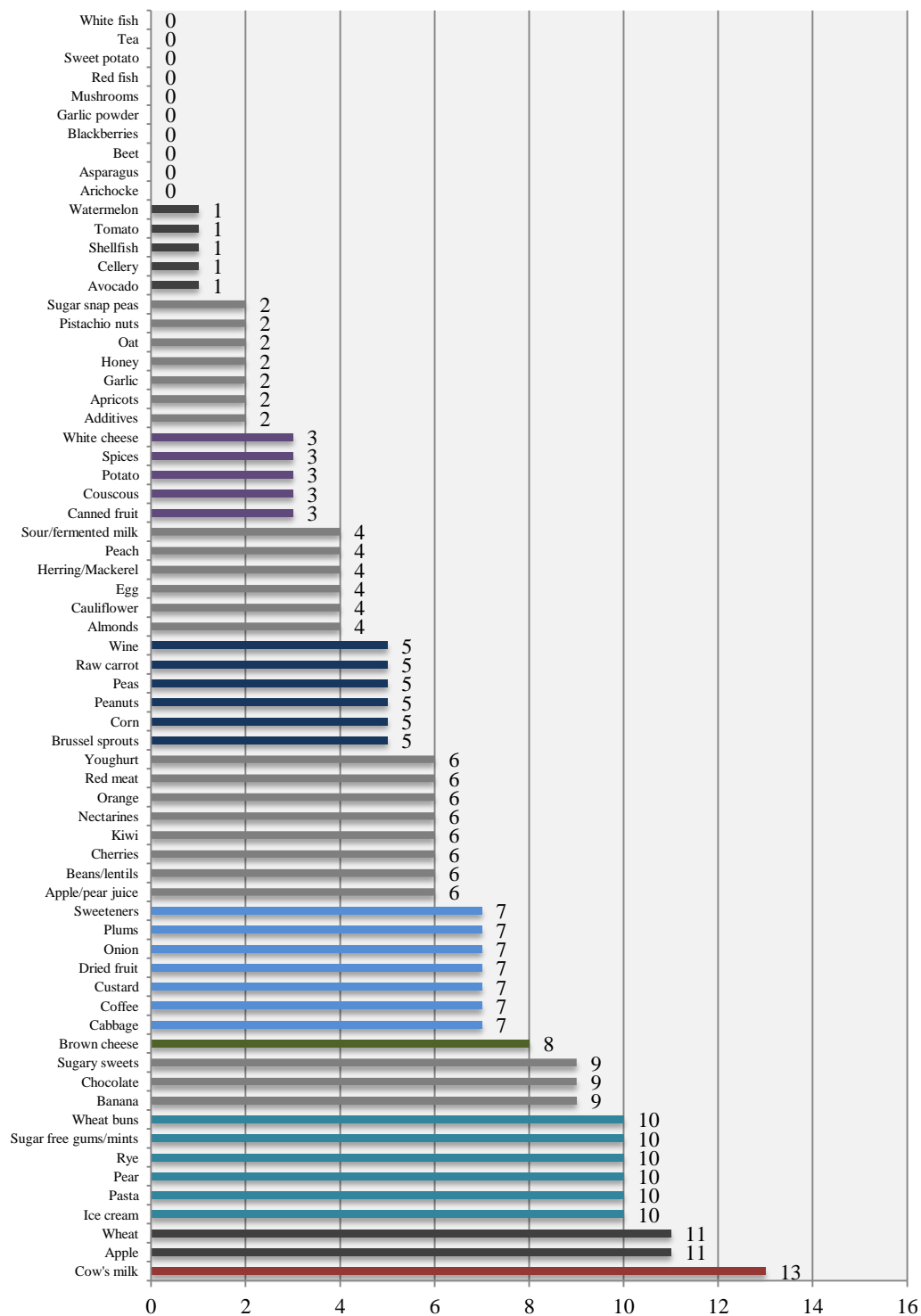


Figure 17. Number of patients reporting food-items as symptom triggers at the food- and symptom recall



## Appendix 15.

Sample of one week of one patient's baseline period

Figure 18 illustrates the baseline period week one in one patient. As seen, the symptom severity of the seven symptoms reported at the VAS was quite different from day to day.

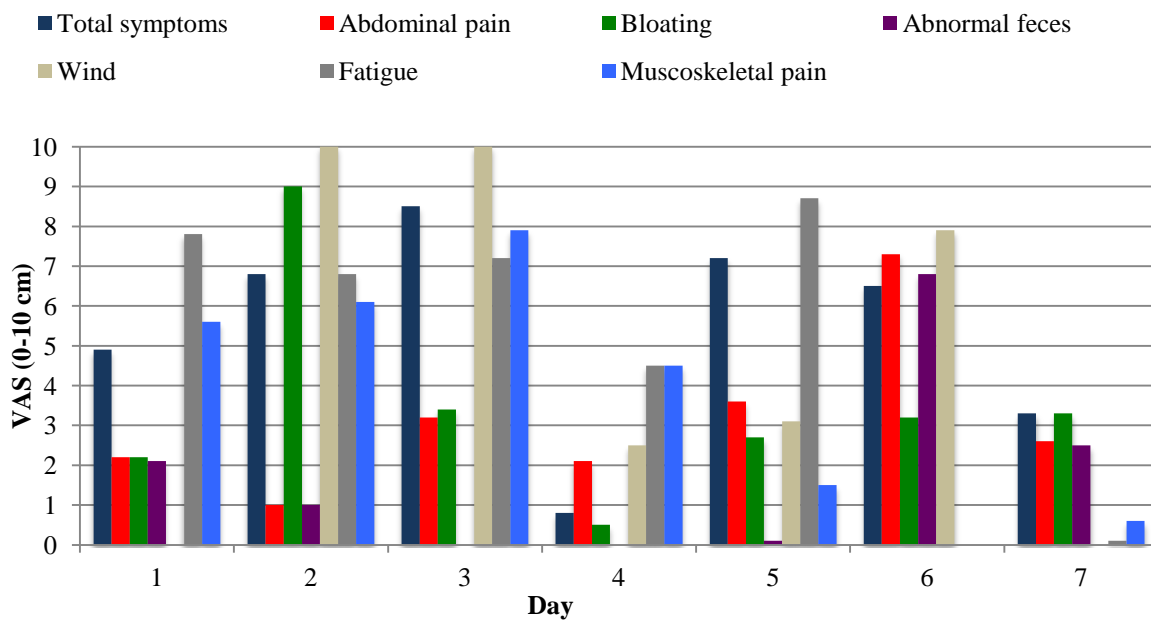


Figure 18. Baseline period week one in one patient



## Appendix 16.

Sample of one 'responder' vs one 'non-responder'.

The following figures 19 and 20 show the mean of the median VAS scores obtained in all symptoms in four different weeks in one patient; baseline week one and two and elimination week one and two. Figure 19 presents the one patient who seemed not to respond to the elimination diet. The symptom severity did not decrease noticeably from baseline to the elimination period. This patient is hence called a 'non-responder.' Importantly, there seemed to be only one patient that did not respond to the elimination diet.

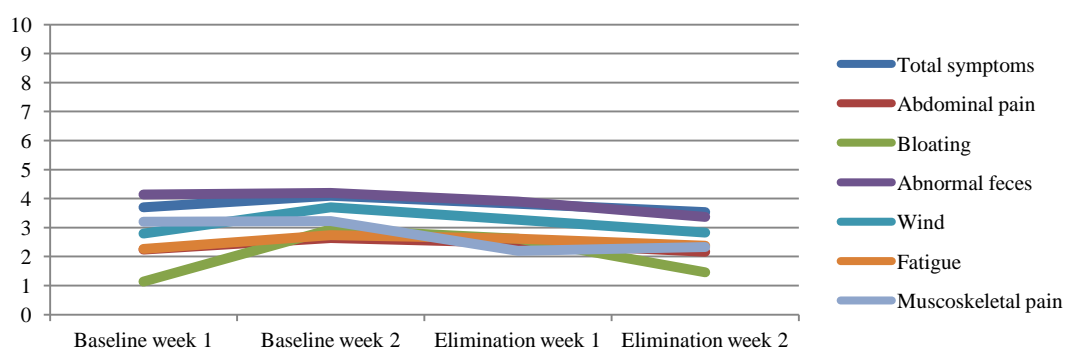


Figure 19. The first four weeks of the study intervention in one 'non-responder'

Contrary to figure 19, figure 20 illustrates one patient who had a markedly decrease from baseline to the elimination period. As seen, all symptoms decreased from the baseline period to the elimination period. This patient is called a 'responder.'

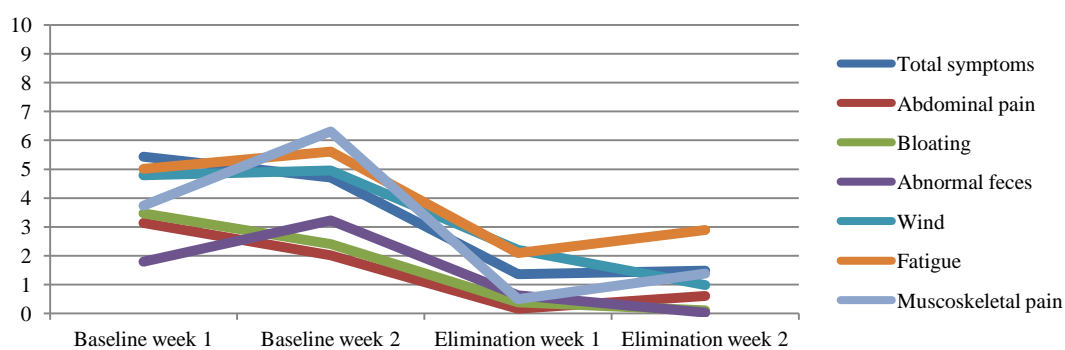


Figure 20. The first four weeks of the study intervention in one 'responder'