# The Role of Diet in Irritable Bowel Syndrome with special reference to Gut Neuroendocrine System

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# Scientific environment



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# **ABSTRACT**

**Background:** The majority of the patients with irritable bowel syndrome (IBS) believe that diet triggers their symptoms, which affect the quality of their lives. The pathophysiology of IBS is not exactly known, however, the endocrine cells of the gut, which are known to regulate most of the functions of the gastrointestinal tract, are believed to play an important role in the IBS pathophysiology. These cells have been found abnormal in the patients with IBS. These endocrine cells extend their microvilli to the gut lumen and sense its contents, particularly nutrients, and release gut hormones in response to the events taking place in the gut lumen.

**Aim:** The overall aim has been to investigate the effect of dietary guidance with reduced intake of fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) on:

- 1. IBS symptoms.
- 2. The quality of life of IBS patients.
- 3. To elucidate whether the changes in symptoms and quality of life brought by dietary guidance are accompanied by alterations in the gastrointestinal endocrine cells.

Materials and methods: Forty-six patients who fulfilled the Rome III criteria for the diagnosis of IBS were included in the study. All the patients were asked to complete the following questionnaires to assess their symptoms, quality of life and habitual dietary intake: The Birmingham IBS symptom score questionnaire, the IBS Quality of Life (IBS-QOL) questionnaire, the Short-Form Nepean and Dyspepsia Index (SF-NDI) and the MoBa Food Frequency Questionnaire (MoBa FFQ). They also underwent gastroscopy with biopsies taken from the corpus and the antrum of the stomach and colonoscopy with biopsies taken from the colon and the rectum to exclude other organic diseases. Then the patients attended three sessions,

approximately 45 minutes each, of guidance on dietary management with a registered nurse. Of these patients, only 17 patients remained during the whole study and were asked to strictly follow a diet as prescribed in the dietary guidance for at least 3 months. Thereafter, they were asked to complete a second set of the same questionnaires for comparison. Fourteen out of the 17 patients underwent a second gastroscopy with biopsy samples taken from the corpus and antrum of the stomach and 13 out of the 17 patients underwent a second colonoscopy with biopsy samples taken from the colon and the rectum. As controls, 14 healthy subjects were included and underwent gastroscopy with biopsy sampling same as the patients. Only 13 out of the 14 controls underwent colonoscopy with biopsy sampling similar to the ones taken from the patients. The biopsy samples were immunostained using the Avidin-biotin-Complex method for all of the endocrine cell types in the stomach and the large intestine and were quantified by computerized image analysis.

**Results:** The findings are summarized as follows:

In paper I, the patients reported an improvement in their quality of life as assessed by IBS-QOL and the SF-NDI questionnaires and a reduction in the total IBS symptoms as assessed by the Birmingham IBS symptom score questionnaire. There was a reduction in the consumption of food items rich with FODMAPs and an increase in the consumption of some minerals and vitamins.

In paper II, IBS patients had low densities of chromogranin A (CgA) in the stomach. These densities increased in these patients following dietary guidance towards the levels of healthy controls.

In paper III, the densities of all the endocrine cells in the stomach of IBS patients were abnormal before receiving dietary guidance. These densities changed towards the values of healthy controls after receiving dietary guidance.

In paper IV, IBS patients represented low densities of CgA in the colon and were increased towards the values of healthy controls following dietary guidance. The

densities of CgA in the rectum were unchanged before and after receiving dietary guidance.

In paper V, the densities of the endocrine cells in the colon of IBS patients were abnormal before dietary guidance. Following dietary guidance, the densities of the endocrine cells tend to normalize in the colon, however, in the rectum; the densities of the endocrine cells remained unchanged.

#### **Conclusions:**

Three sessions of dietary guidance reduced the symptoms of IBS patients and improved their quality of life. Through dietary guidance, the patients made correct choices in consuming a FODMAP-poor diet yet maintaining adequate intake of minerals and vitamins that were, otherwise, known to be deficient in IBS patients without guidance. The densities of the endocrine cells in the stomach and the large intestine that were abnormal before dietary guidance tend to normalize following dietary guidance, thus reducing IBS symptoms and improving the quality of life of the patients. The findings emphasized the interactions between food and the endocrine cells of the gut and showed the positive effects of dietary guidance on the symptoms of IBS patients, which may be attributed to changes in the densities of the endocrine cells of the gut.

# LIST OF ABBREVIATIONS

CCK Cholecystokinin

CgA Chromogranin A

CNS Central nervous system

DAB Diaminobenzidine

ENS Enteric nervous system

FFQ Food Frequency Questionnaire

FGIDs Functional gastrointestinal diseases

FODMAPs Fermentable oligo-, di- and monosaccharides and polyols

FOS Fructo-oligosaccharides

GI Gastrointestinal

GIP Gastric inhibitory peptide

GOS Galacto-oligosaccharides

HLA Human leukocyte antigen

HRQoL Health related quality of life

IBS Irritable bowel syndrome

IBS-D IBS-diarrhea

IBS-C IBS-constipation

IBS-M IBS-mixed

NES Neuroendocrine system

NPY Neuropeptide Y

NO Nitric oxide

PP Pancreatic polypeptide

PPI Proton pump inhibitors

PYY Polypeptide YY

QOL Quality of Life

SEM Standard error of mean

SERT Serotonin transporter

SF-NDI Short-Form Nepean and Dyspepsia Index

SIBO Small intestinal bacterial overgrowth

VIP Vasoactive inhibitory polypeptide

# LIST OF PUBLICATIONS

- I. Mazzawi T, Hausken T, Gundersen D, El-Salhy M 2013 Effects of dietary guidance on the symptoms, quality of life and habitual dietary intake of patients with irritable bowel syndrome. Molecular Medicine Reports 8(3):845-852
- II. Mazzawi T, Gundersen D, Hausken T, El-Salhy M 2014 Increased gastric Chromogranin A cell density following changes in diet intake in patients with irritable bowel syndrome. Molecular Medicine Reports 10(5):2322-2336
- III. Mazzawi T, Hausken T, Gundersen D, El-Salhy M 2015 Effect of dietary management on the gastric endocrine cells in patients with irritable bowel syndrome. European Journal of Clinical Nutrition 69, 519–524
- IV. Mazzawi T, Gundersen D, Hausken T, El-Salhy M 2015 Increased chromogranin A cell density in the large intestine of patients with irritable bowel syndrome after receiving dietary guidance. Gastroenterology research and practice (ID 823897)
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#### 1. INTRODUCTION

### 1.1 Irritable bowel syndrome

#### 1.1.1 General

Irritable bowel syndrome (IBS) is a common chronic functional disorder of the gastrointestinal (GI) tract (1-3). It occurs more frequently in women than in men and is more common under the age of 50 (4-10). IBS accounts for approximately 12-14% of the referrals to general practitioners and for 25-28% to gastroenterologists (3, 11-13) and is considered the most common gastrointestinal diagnosis in general practice (14). In fact, IBS is even a more common reason to seek medical care than diabetes, hypertension and asthma (11, 12, 15).

Despite the fact that IBS neither develops into serious diseases such as cancer or inflammatory bowel disease (16, 17) nor is associated with increased mortality (18), IBS can be as morbid as major chronic diseases, such as congestive heart failure (19), hepatic cirrhosis (20), renal insufficiency and diabetes (10). The symptom intensity differs considerably between the patients from mild to severe, and from daily to intermittent (weekly or monthly), thus affecting the patients' daily activities and reducing their quality of life (3, 5, 8, 21-25). IBS has a negative impact on several aspects of the patient's life such as sleep, diet, work, leisure, travel, sexual activity and mood (depression/anxiety) (26). Patients with IBS have lower productivity at work/school due to their frequent absences (5, 12, 26-28), and more frequently change, lose or quit their jobs and turn down promotions (12, 26). In addition to the previously mentioned impaired productivity, the patients generate high cost on health-care sectors for undergoing more diagnostics tests, frequent visits to the doctor's office, recurrent hospitalizations and they consume more medications than those without IBS (26). The annual direct and indirect costs to mange these patients are

estimated at 15-30 billion US dollars (29-33). Hence, IBS imposes an economic burden on the society and the patients (19, 24, 29, 31, 34-36).

#### 1.1.2 Prevalence

Using symptom-based diagnosis, the prevalence of IBS is estimated as 5-20% of the population worldwide (1, 3, 5, 7-9, 21-23, 25, 31, 34, 37). The prevalence of IBS differs depending on the used criteria (highest using Manning, and lowest using Rome II) (8, 38-41) and it shows a geographical variation (8). Using Rome II criteria, the prevalence of IBS in Europe is 11.5% (8), Canada 12.1% (42), USA 4.7% (38), Australia 6.9% (43), Egypt 34% (44) and China 4.6-5.6% (45). In Scandinavia, the prevalence of IBS in Denmark is 10.5% (46) and Sweden 14.5% (47). In Norway, on the other hand, the first population-based survey of IBS was performed in Tromsø in 1980 and showed a prevalence of 8% (48). A later study conducted in southern Norway (Oppland and Hedmark) using Rome II criteria for diagnosing IBS showed a similar prevalence of IBS (8.4%) (49) however, another study performed in northern Norway (Bodø and Sørreisa) using the same criteria resulted in a prevalence of 25.1% (50).

# 1.1.3 Diagnosis

To date, the diagnosis of IBS is based on the presenting symptoms due to the lack of biochemical, histopathological or radiological diagnostic tests (2, 3, 51, 52). IBS is characterized by a complex of symptoms; including abdominal pain or discomfort, bloating, and alterations of bowel movements (1, 3, 26, 51). Depending on the predominant bowel habit, the patients with IBS are classified into diarrheapredominant (IBS-D), constipation-predominant (IBS-C) and mixed (diarrhea and constipation, IBS-M) (39, 53).

Several symptom-based diagnostic criteria have been developed for the diagnosis of IBS (51, 54-59) starting with Manning criteria (Table 1) in 1978 (54). The latest

developed criteria are Rome I in 1992 (60), updated to Rome II in 1999 (28) which were then followed by Rome III criteria (Table 2) in 2006 (51).

#### Table 1. Manning criteria for the diagnosis of irritable bowel syndrome

- Abdominal pain that is improved by defecation
- Stools are more frequent at onset of pain
- Stools are looser at onset of pain
- Visible abdominal distension
- Mucous passing per rectum
- Feeling of incomplete evacuation

#### Table 2. Rome III criteria for the diagnosis of irritable bowel syndrome

Recurrent abdomen pain/discomfort occurring at least 3 days/month in the past 3 months with symptom onset at least 6 months prior to diagnosis, associated with two or more of the following:

- Relieved with defecation; and/or
- Onset associated with a change in the frequency of the stool; and/or
- Onset associated with a change in the form (appearance) of the stool.

Cumulatively supporting symptoms for the diagnosis of IBS:

- Abnormal frequency of the bowel movements (> 3/day and < 3/week);
- Abnormal form of the stool (lumpy/hard or loose/watery stool);
- Abnormal passage of the stool (straining, urgency, or feeling of incomplete evacuation);
- · Mucous passage;
- Bloating or feeling of distention of the abdomen.

# 1.1.4 Pathogenesis

The pathogenesis of IBS is complex and multifactorial (34). The factors that either solely or through interactions with each other (Fig. 1), seem to play role in the pathogenesis of IBS, are: hereditary, mucosal low-grade inflammation, intestinal microbiota, abnormal endocrine cells of the gut, and diet, as summarized in Table 3.

Food allergy has been suggested to play a role in the pathogenesis of IBS, however, allergic reactions to food are mediated by immunoglobulin E causing acute swelling, itching, hives, diarrhea, wheezing and/or collapse and no consistent evidence has shown such allergic manifestations in IBS (61-64).

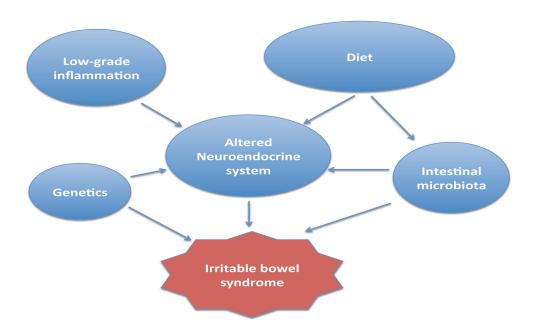


Figure 1. A schematic illustration of possible pathogenesis in irritable bowel syndrome.

Table 3. Factors believed to play a role in the pathogenesis of irritable bowel syndrome.

Factor	Definition/ Importance	Reason/ Mechanism
Hereditary	Double or triple the risk in	Over 60 candidate genes
	first grade relatives (65).	are associated with IBS
	Occurs more frequent in	(67).
	monozygote twins (22.4%)	
	than dizygote twins (9.1%)	
	(66).	
Low-grade inflammation	- Post-infectious IBS due	- Post-infectious IBS:
	to gastroenteritis caused by	rectal biopsies showed
	different pathogens: C.	increased leucocytes,
	jejuni, Salmonella	lymphocytes, mast cells
	enterica, Shigella sonnei,	and changes in endocrine
	E. coli, Norovirus, and	cell densities (67).
	Giardia lamblia.(68, 69).	
	- Inflammatory bowel	- Occurs in 33-46% of
	diseases (ulcerative colitis	ulcerative colitis in
	and Crohn's disease).	remission (70, 71) and 42-
		60% of Crohn's disease in
		remission (72, 73).
Intestinal microbiota	Crucial for normal	- Low Bifidobacteria and
	physiological and	Lactobacillus in IBS (76).
	immunological functions	- Changes in intestinal
	of the GI tract (74, 75).	microbiota can cause
	Microbiota are affected by	visceral hypersensitivity,
	diet, antibiotics, stress,	changed intestinal motility,

Table 3. (Continued)

Factor	Definition/ Importance	Reason/ Mechanism
	genetics, age, infections	flatulence and low-grade
	genetics, age, infections	maturence and low-grade
	and climate changes (77).	inflammation (78).
		- Small intestinal bacterial
		overgrowth (SIBO) can
		cause IBS symptoms (79).
Endocrine cells of the gut	Abnormal densities and	Caused by diet, stress,
	functions leading to	low-grade inflammation,
	release of different gut	and genes, (will be
	hormones, (will be	discussed further).
	discussed further).	
Diet	Carbohydrates, fibers and	Fermentation causes gas
	fat, (will be discussed	production and increased
	further).	osmosis into the gut lumen
		leading to diarrhea, (will
		be discussed further).

#### 1.2 Diets in IBS

Food plays a vital role in the development of IBS symptoms (61, 80-86) and the majority of IBS patients are primarily interested in knowing what foods to avoid (82, 87). The elapsed time from food consumption until the appearance of IBS symptoms varies between the patients; 28% of the patients experienced symptoms within 15 min of eating and 93% reported symptom worsening between 15 min and 3 h (80). More than two thirds of the IBS patients link their symptoms to specific food items (61, 80, 81), most commonly milk and other dairy products, wheat products, caffeine, certain meat, cabbage, onion, peas/beans, tomatoes, hot spices, fried foods (12, 24, 80, 88),

raw vegetables, raw broccoli, paprika, leeks, garlic, and mushrooms (24). These foods are rich in the poorly absorbed rapidly fermentable oligo-, di- and monosacharides and polyols (FODMAPs) (12, 24, 89-91).

#### 1.2.1 FODMAPs

Carbohydrates are considered a major source of energy for humans, with intakes ranging from 40% to 80% of total energy requirements (90). Dietary carbohydrates can be divided into short-chain (sugars, polyols and oligosaccharides) and long-chain carbohydrates (starch, resistant starch and non-starch polysaccharides) (89). Long-chain carbohydrates have beneficial effects on fecal bulking, faster colonic transit time and slight acidification of the luminal milieu (89). On the other hand, the short-chain carbohydrates are referred to as prebiotics because they stimulate the growth of beneficial bacteria of the colon, bifidobacteria and lactobacillus. The short-chain carbohydrates include fructans [fructo-oligosaccharides (FOS) and inulin] and galacto-oligosaccharides (GOS), Table 4 (89, 92). These prebiotics have a wide range of benefits including reducing the risk of gastrointestinal infections, improving laxation and calcium absorption, preserving the gut mucosal barrier and stimulating the immune system of the GI tract which may reduce the risk of colon cancer (in animals) (89).

Table 4. FODMAPs found in some food varieties

FODMAPs	Examples of foods	
- Lactose	- Milk	
- Fructose in excess of glucose	- Pears, apples and honey	
- Fructans and FOS	- Artichoke, garlic, onions, rye, wheat,	
	pasta, breads and breakfast cereals	
- GOS (stachyose and raffinose)	- Pulses	
- Polyols (mannitol and sorbitol)	- Stone fruits and artificial sweeteners	

During the fermentation of the long-chain carbohydrates, the intestinal flora in the colon ferments the undigested carbohydrates to produce gases (carbon dioxide, hydrogen and/or methane) and short chain fatty acids (89, 93, 94). In addition, poorly absorbed short-chain carbohydrates increase the volume of fluid in the bowel through osmosis (89, 94, 95), which results in a natural laxative effect in healthy individuals (89). However, in IBS patients, these reactions may cause diarrhea, and in association with the produced gas may lead to luminal distension with symptoms of abdominal pain and bloating (89, 93, 94, 96). It is worth mentioning that the total content of FODMAPs is important in the development of IBS symptoms, not just the presence of specific types (83, 89, 90). Some foods contain several FODMAPs, for example, white onion contains excess fructose, raffinose, nystose, and kestose, which are particularly problematic for people with IBS (90). It is important to note that, in terms of the total content of a major FODMAP, the major clinical problem is likely to generate from fructans in vegetables and from free fructose and sorbitol (to a lesser extent) in fruits (90).

#### 1.2.2 Fibers

Dietary fibers are defined as the sum of indigestible polysaccharides and lignin. They are derived from cell wall contents in most diets and are found in cereals, vegetables, fruits and nuts (97).

Fibers are divided into water-soluble and water insoluble according to their water holding capacity. Fibers with high water holding capacity such as pectin, gums and psyllium are called water-soluble. They account for 4-21% of dietary fiber in cereal bran and 19-59% in legumes, vegetables and fruits. Oat is more highly rich in water-soluble fibers than any other grain. Wheat, rye, rice and most other grains are primarily composed of insoluble fiber, while legumes and beans contain both water-soluble and insoluble fibers (97).

Foods containing a higher proportion of dietary fiber, especially water-soluble fibers, can lead to the prevention of diseases such as coronary heart disease, diabetes, irritable bowel disease, obesity and colon cancer (97). Viscous polysaccharides act in the gastrointestinal tract and decrease the absorption of biliary cholesterol and cholesterol or fatty acids thus reducing blood cholesterol. Dietary fibers increase the secretion of bile acid and cholesterol thus having a hypocholesterolemic effect. Short chain fatty acids, which result from the colonic fermentation of resistant starch, may help in reducing blood cholesterol levels therefore reducing the risk of coronary heart diseases. Resistant starch is found in whole or partly milled grains and seeds, pulses and corn flakes. Fibers have also beneficial effects in diabetes; soluble fibers help in reducing the insulin demand by slowing the absorption and digestion of carbohydrates, and insoluble fibers shortens intestinal transit time therefore allowing less time for the absorption of carbohydrates (97).

Fibers have been used as a bulking agent for treatment of IBS (82, 97); however, the use of soluble fiber has the tendency to improve the symptoms of IBS compared to insoluble fiber (82, 98-100). The use of insoluble fiber may worsen IBS symptoms (82, 98), causing bloating and abdominal discomfort (101). For example, it is recommended to use psyllium (mostly water-soluble fibers) over bran (water insoluble fibers) in IBS patients to alleviate their symptoms (101).

#### 1.2.3 Fat

The lipolysis of triglycerides (>12 carbon atoms) begins in the stomach by gastric lipase and is completed in the duodenum by pancreatic lipase thus releasing fatty acids and monoglycerides. The process of digestion is initiated with the formation of emulsions of finely dispersed lipids that bind to lipase. The lipid components (fatty acids and monoglycerides) then form water-soluble micelles with conjugated bile acids and are absorbed across the enterocyte membrane. Thereafter, triglycerides are reassembled and incorporated into chylomicrons and transported in the lymphatic system. Medium-chain triglycerides (8–12 carbon atoms) are absorbed directly into

the bloodstream without luminal lipolysis and micelle formation. Fat is digested and completely absorbed in the small bowel, thus, normally no dietary fat enters the colon. Colonic bacteria ferment the unabsorbed carbohydrates producing short-chain fatty acids (< 8 carbon atoms), which are an important source of energy for colonocytes, as well as for the colonic microbiota (102).

Fat intake modulates GI function in healthy individuals (102). Different meal types with different caloric contents activate several braking systems in the GI tract at different rates (103-105). In healthy individuals, fat slows gastric emptying and lipid in the duodenum stimulates pyloric pressure (102, 104) and increases the biliopancreatic secretion (106). The consumption of fat-rich meals (102) activates the gastroduodenal brake by inhibiting gastric emptying (102, 107) and decreasing pyloric pressures (108). The presence of fat in the proximal small intestine promotes a jejunal brake to decrease the biliopancreatic secretions (105, 106) and to inhibit the intestinal transit (109). In addition to the jejunal brake, an ileal brake is activated upon the arrival of fat to the ileum (110), thus allowing more time for fat digestion and absorption and avoiding its loss into the colon (109). The jejunal and ileal brakes are mediated by different gut hormones (109, 110), which will be discussed further in other sections of the thesis.

Fat modulates the gut response to different stimuli (102). Patients with functional gastrointestinal diseases (FGIDs) such as IBS, have abnormal lipid-dependent motor dysfunction affecting the small intestine and sparing the colon (111). For example, they have increased sensitivity to lipid exposure in the small intestine, which induces symptoms of bloating (102, 111), fullness and nausea at lower nutrients loads, and enhances gut sensitivity to mechanical distension (102). Intraluminal fat in patients with IBS impairs gas transit and develop gas retention and abdominal distension in the small intestine (especially in the jejunum) rather than the colon (111). The effects of lipids on small intestinal motility and delaying the transit of gas through the intestines are ineffective in healthy individuals but result in gas retention and bloating in IBS

patients (111). Lipids also exacerbate rectal hypersensitivity (102, 112) and increase the perception of rectal distension in IBS patients (102, 113) causing pain in patients with IBS-C but urgency in patients with IBS-D (102).

Although some reports show that a proportion of IBS patients relate their symptoms to fatty foods, no consistent dietary differences in fat consumption have been observed between IBS patients and controls (102).

#### 1.2.4 Protein

The majority of dietary protein is absorbed after being hydrolyzed into amino acids and peptides. Almost 20% of the dietary protein enters and reach the distal colon and is putrefied (fermented) by colonic bacteria producing ammonia, amines, phenols and sulfides (114, 115). Ammonia is essential for the bacterial metabolism and for protein synthesis. In addition, branched chain fatty acids (isovalerate and isobutyrate) (115, 116) and short chain fatty acids (butyrate) from amino acids reductive deamination (115, 117) are produced at the distal colon in the absence of carbohydrate fermentation (which occurs at the proximal colon) (115). Another product of protein putrefaction is sulphur-containing gas (hydrogen sulphide) which gives a foul odor (114). Products of the protein putrefaction are potentially harmful, phenols are carcinogenic for other systems and hydrogen sulphide is toxic to the epithelium. However, concerning IBS, only the malodourous flatus is of concern to the patients and no certain effects of malabsorbed proteins on intestinal motility or visceral hypersensitivity is known (114).

Gluten is a group of proteins found in wheat, barely and rye and is the cause of coeliac disease presenting with symptoms mimicking IBS (114). The intake of gluten causes the activation of the immune system that leads to a change in the mucosal barrier function causing increased intestinal permeability. A gluten-free diet usually reduces bowel frequency in human leukocyte antigen (HLA)-DQ2/8 positive patients with diarrhea-predominant IBS (IBS-D) due to the reduction of the intestinal permeability

(118). In addition, a gluten-free diet improves symptoms of IBS due to the reduction of FODMAPs in wheat rather than gluten in foods where gluten is also a common component (119).

#### 1.2.5 Food chemicals

Natural chemicals such as amines, glutamates and salicylates occur in foods. Salicylates are found in plants whereas amines and glutamates are products of protein breakdown in animal meat (120). Food additives such as glutamates are used as flavor enhancers, and benzoates, sulfites, and nitrates as preservatives (120). These bioactive chemicals interact with the GI luminal chemoreceptors and influence the function of the enteric nervous system of the gut (114). A low food chemical diet may be beneficial in IBS. There is no evidence if reduction of caffeine or ethanol consumption is beneficial in IBS (114).

#### 1.2.6 Dietary guidance

Most IBS patients believe that diet plays a significant role in the development of their symptoms (80, 81). Therefore, they make a conscious choice to avoid certain food items, some of which belong to the FODMAPs group. However, they tend to consume other food items that are rich in FODMAPs and avoid food sources important to their health (24). A Norwegian study on food intolerance and IBS showed that 62% of its subjects limited or excluded some food items from their daily meals and 12% of them made drastic changes in their diet that could result in nutritional deficiencies in the long run (81). Patients with IBS tend to have low intake of calcium, potassium, magnesium, vitamin A, vitamin B<sub>12</sub> and riboflavin (vitamin B<sub>2</sub>) (24, 121-123). Another Norwegian study, which compared two different groups of IBS patients, where one group received dietary guidance and the other group did not receive guidance, showed that dietary guidance helped in reducing IBS symptoms, improved their quality of life and normalized the patients' consumption of necessary vitamins and minerals thus avoiding deficiencies (24). Several studies were performed based on

a FODMAP-poor diet that resulted in the improvement of the symptoms of IBS patients (86, 93, 94, 124-129).

# 1.3 Endocrine cells of the gut

Several functions of the gastrointestinal tract, such as motility, secretion, absorption, microcirculation, local immune defense and cell proliferation and food intake, are controlled and regulated by a local regulatory system; the neuroendocrine system (NES) of the gut. This regulatory system is independent of the central nervous system (CNS), but communicate and integrate with it (34, 130-135).

The NES consists of two parts: a) the endocrine cells of the gut and b) the enteric nervous system (ENS) including peptidergic-, serotonergic- and nitric oxide containing nerves in the gut walls, Fig. 2 (12). The different parts of the NES interact and integrate with each other and with the afferent and the efferent neurons of the CNS, particularly the autonomic nervous system (34, 130, 131).

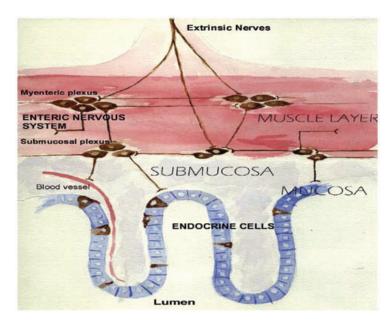
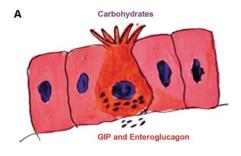
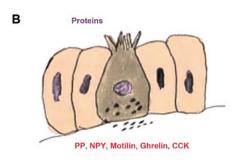


Figure 2: Schematic drawing of the neuroendocrine system (NES).
Reproduced from (12) with permission from the authors and the publisher.

The endocrine cells of the gut, which are scattered among the epithelial lining of the gut lumen (135-138), comprise almost one percent of all epithelial cells in the gut and are considered to be the largest endocrine organ in the body (138-140). All epithelial cell types (including the endocrine cells) originate from pluripotent stem cells of an endodermal origin (141-150). The differentiation of stem cells into endocrine cells in the gut is rapid, over a period of 2-4 days (151, 152). The endocrine cells project specialized microvilli into the lumen, which sense the luminal contents (mainly nutrients) and release specific hormones into the lamina propria (135, 136, 153-163). There are at least 15 different types of endocrine cells in the GI tract based on the types of hormones they release (34, 144), Table 5 (12, 34). The types of released hormones depend on the types of sensed nutrients (carbohydrates, fat and proteins) (34, 130, 164), Fig. 3 (164). These hormones exert their effect through different modes of action: endocrine (through blood circulation to distant targets), paracrine/autocrine (locally), synaptic signaling or by neuroendocrine means (being released from synapses into blood circulation) (34, 130, 131, 164).





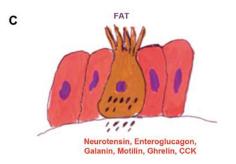


Figure 3. The gut hormones released into the interstitial fluid of the lamina propria in response to intraluminal nutrient content vary according to the proportions of (A) carbohydrates, (B) proteins and (C) fats. These hormones may act in an endocrine/paracrine manner or as neurotransmitters/neuromodulators of neurons in the ENS. Reproduced from (164) with permission from the authors and the publisher.

The different types of endocrine cells are located either in specific areas of the gut or throughout the gut (130, 144, 164, 165). Serotonin- and somatostatin-producing cells are found throughout the GI tract, while ghrelin- and gastrin-producing cells are found in the stomach and those producing polypeptide YY (PYY) and oxyntomodulin (enteroglucagon) are located in the lower small and large intestines (130, 144, 164, 165).

Table 5. Hormones of the endocrine cells of the gastrointestinal tract.

Hormone	Function	Mode of action	Cellular origin	Released by
Gastrin	Stimulates gastric	Endocrine.	Gastric G-cell.	Intraluminal
	acid secretion			peptides;
	and histamine			amino-acids;
	release; trophic			calcium;
	action on gastric			catecolamines;
	mucosa and			low pH and
	stimulates			prostaglandins.
	contraction of			
	lower esophageal			
	sphincter and			
	antrum.			
Ghrelin	Ghrelin increases	Endocrine.	Gastric oxyntic	Protein and fat
	appetite and		X/A cell.	ingestion.
	feeding;			Suppressed by
	stimulates gastric			carbohydrate
	and intestinal			ingestion.
	motility.			
Secretin	Stimulates	Endocrine.	Intestinal S cell.	Acidification.
	pancreatic			Inhibited by
	bicarbonate and			somatostatin.
	fluid secretion;			
	inhibits gastric			
	emptying; and			
	inhibits			
	contractile			
	activity of small			
	and large			
	intestine.			

Table 5. (Continued)

Hormone	Function	Mode of action	Cellular origin	Released by
Somatostatin	Inhibits intestinal	Paracrine,	Gastric and	Mixed meal
	contraction, gut	endocrine.	intestinal D cell,	and
	exocrine and		myenteric and	acidification of
	neuroendocrine		submucosal	the stomach.
	secretions.		neurons.	
Oxyntomodulin	Inhibits gastric	Endocrine.	Intestinal L cell.	Intraluminal
(enteroglucagon)	and pancreatic			carbohydrates
	secretions.			and fat.
Serotonin	Stimulates gastric	Paracrine	Enterochromaffin	Noradrenalin;
	antrum, small	mediator,	cells, myenteric	acetylcholine;
	intestinal and	transmitter.	and submucosal	acidification
	colonic motility.		neurons.	and
				intraluminal
				pressure.
Peptide YY	Major 'ileal	Endocrine,	Intestinal H/L	Protein- rich
(PYY)	brake' mediator.	paracrine.	cell.	meal.
	Delays gastric			
	emptying;			
	inhibits gastric			
	and pancreatic			
	secretion.			
Pancreatic	Inhibits	Endocrine.	Intestinal PP cell	Protein- rich
polypeptide (PP)	pancreatic			meal.
	secretion; relaxes			
	gall bladder; and			
	stimulates			
	motility of			
	stomach and			
	small intestine.			

Table 5. (Continued)

Hormone	Function	Mode of action	Cellular origin	Released by
Neuropeptide Y	Causes	Transmitter,	Myenteric and	Protein- rich
(NPY)	vasoconstriction.	mediator.	submucosal	meal.
	Inhibits		neurons.	
	pancreatic and			
	intestinal			
	secretions;			
	reduces			
	gastrointestinal			
	motility.			
Motilin	Induces phase III	Endocrine.	Intestinal M cell.	Protein and fat.
	migrating motor			
	complex.			
Cholecystokinin	Inhibits gastric	Endocrine	Intestinal I cells,	Intraluminal
(CKK)	emptying;	transmitter?	myenteric and	protein and fat.
	stimulates gall		submucosal	Inhibited by
	bladder		neurons.	somatostatin.
	contraction,			
	intestinal motility			
	and pancreatic			
	exocrine			
	secretion;			
	stimulates			
	growth; and			
	regulates food			
	intake.			
Gastric	Incretin. Inhibits	Endocrine.	Small intestinal	Intraluminal
inhibitory	gastric acid		cells.	glucose,
peptide (GIP)	secretion.			amino-acids
				and fat.

Table 5. (Continued)

Hormone	Function	Mode of action	Cellular origin	Released by
Vasoactive	Causes	Transmitter,	Myenteric and	Serotonin.
inhibitory	vasodilation.	mediator.	submucosal	
polypeptide	Stimulates GI		neurons.	
(VIP)	and pancreatic			
	secretions;			
	relaxes smooth			
	muscles of the			
	gut.			
Neurotensin	Stimulates	Endocrine	Intestinal N cell,	Fat.
	pancreatic	transmitter,	myenteric and	
	secretion; inhibits	mediator.	submucosal	
	gastric secretion;		neurons.	
	delays gastric			
	emptying; and			
	stimulates			
	colonic motility.			
Galanin	Inhibits gastric,	Transmitter,	Myenteric and	Fat.
	pancreatic and	mediator.	submucosal	
	intestinal		neurons.	
	secretions; delays			
	gastric emptying			
	and intestinal			
	transit; and			
	suppresses			
	postprandial			
	release of some			
	neuroendocrine			
	peptides.			

Table 5. (Continued)

Hormone	Function	Mode of action	Cellular origin	Released by
Substance P	Causes	Transmitter,	Myenteric and	Gut distention.
	vasodilation.	mediator.	submucosal	
	Stimulates		neurons.	
	smooth muscle			
	contraction; and			
	inhibits gastric			
	acid secretion.			
Nitric oxide	Relaxation of	Transmitter.	Myenteric and	Activation of
(NO)	smooth muscle.		submucosal	protein kinase
			neurons.	C alpha and/or
				epsilon.

# 1.4 Interaction between diet and endocrine cells of the gut

The release of different gut hormones is triggered by different nutrients in the gut lumen. Proteins and fat trigger the release of serotonin, somatostatin, ghrelin and PYY and carbohydrates suppress ghrelin release, while carbohydrates and fat trigger the release of oxyntomodulin (enteroglucagon) (164), Fig. 3. The gut endocrine cells, their locations, mode of action and functions are summarized in Table 5. The endocrine cell types discussed in this thesis shall be touched upon briefly.

Chromogranin A (CgA) is a member of the granin (chromogranin-secretogranin) family and is located within the vesicles of neurons and endocrine cells (166-168). CgA is considered to be a common marker for the endocrine cells of the gut and endocrine tumors (166, 167, 169, 170).

Ghrelin is produced primarily by the endocrine cells in the oxyntic mucosa of the stomach. Ghrelin accelerates gastric as well as small- and large-intestinal motility, stimulates the secretion of gastric acid (136, 164, 171-181) and plays an important

role in releasing growth hormone and in regulating appetite and energy metabolism (164, 182-185).

Gastrin is the main hormonal stimulant of gastric acid secretion (164, 186, 187). It also stimulates histamine release and the contractions of the lower esophageal sphincter and antrum (164). The release of gastrin is inhibited by somatostatin (164).

Serotonin is a paracrine messenger used by the enterochromaffin cells as a sensory transducer. It also activates the submucosal sensory branch (Meissner's plexus) of the enteric nerve, which conveys sensation from the gut to the CNS and modulates the gut's visceral sensitivity (164, 188-193). Serotonin stimulates large intestinal motility, accelerates transit through both the small and large intestines (164, 188-196) and inhibits gastric emptying and gastric acid secretion (164).

Somatostatin inhibits intestinal contraction (major 'ileal brake' mediator) and inhibits gastrointestinal exocrine and neuroendocrine secretion (34, 130, 164). It also delays gastric emptying, inhibits gastric acid secretion and stimulates the absorption of water and electrolytes in the large intestine (164).

PYY is considered a major 'ileal brake' mediator (164, 197). In addition, it stimulates the absorption of water and electrolytes, and delays gastric emptying (164).

There is an increasing body of evidence that IBS may be a disorder of the NES of the GI tract and the densities of different types of endocrine cells throughout the different segments of the GI tract have been found to be abnormal in IBS patients (3, 52, 136, 170, 197-204). An altered NES is responsible for abnormal functions of the GI tract such as sensation (visceral hypersensitivity), dysmotility and abnormal secretion, Table 6, all of which are the characteristics of IBS.

Table 6: Abnormalities of the GI tract functions in IBS.

Abnormality	Definition	Proposed mechanisms
Visceral	Reduced pain threshold in	1) Gut-brain axis
hypersensitivity	the bowel during rectal	(parasympathetic and
	balloon dilatation (rectal	sympathetic nervous
	hypersensitivity) or other	systems) (52).
	methods that increase	2) Changes in serotonin
	pressure in the bowels	metabolism by serotonin
	viscera (205, 206).	transporter (reduced
		SERT) (207, 208).
		3) Abnormal endocrine
		cells of the gut (serotonin
		cell densities) (52, 209).
Dysmotility	Abnormal bowel motility	- Transit time in small and
	(transit time and bowel	large bowels increases in
	contractions) in IBS (52, 67,	IBS-C and decreases in
	210) that may contribute to	IBS-D (52, 211-217).
	pain and changes in stool	- Abnormal endocrine cells
	pattern (67).	of the gut (ghrelin,
		serotonin, CCK and PYY)
		(52).

Table 6. (Continued)

Abnormality	Definition	Proposed mechanisms
Abnormal secretion	Increased intestinal secretion	- Increased intestinal
	and decreased pancreatic	secretion due to bile acid
	secretion (functional	perfusion in the ileum (52,
	pancreatic insufficiency)	218).
	(52).	- Increased reactivity of
		the small intestinal sensory
		component of the
		migrating motor complex
		in IBS-D (52, 219)
		- Abnormal endocrine cells
		of the gut (CCK and PYY)
		(52).

Due to the fact that the release of different gut hormones is triggered by food, food quantity and composition would be expected to influence the development of IBS symptoms. To date, the interaction between food intake and the GI endocrine cells has not yet been explored.

## 2. AIMS OF THE STUDY

The overall aim of this PhD thesis was to investigate the effect of dietary guidance including a FODMAP-poor diet on the symptoms and quality of life of IBS patients and to verify whether this effect is accompanied by changes in the endocrine cells in the stomach and the large intestine.

The specific aims of the papers included in this thesis were:

#### Paper I

To investigate the effect of dietary guidance by shifting from a typical Norwegian diet to a FODMAP-poor diet, on the symptoms and quality of life and habitual diet of IBS patients.

#### Paper II

To investigate the effect of dietary guidance outlined above on the total gastric endocrine cells as detected by CgA in IBS patients.

#### Paper III

To identify which gastric endocrine cell types are affected after receiving dietary guidance in the same cohort of IBS patients.

## Paper IV

To investigate the effect of dietary guidance mentioned above on the total endocrine cells in the large intestine as detected by CgA in the same cohort of IBS patients.

## Paper V

To determine which types of large intestinal endocrine cells are affected after receiving dietary guidance in the same cohort of IBS patients.

## 3. MATERIALS AND METHODS

#### 3.1 Patients and controls

Patients who were referred to the section of gastroenterology at Stord Helse-Fonna Hospital (Stord, Norway), who fulfilled the Rome III criteria for the diagnosis of IBS were included in the study. Patients of both genders and aged between 18 and 70 years were included. Exclusion criteria comprised the presence of organic gastrointestinal or other systemic diseases, women who were pregnant or lactating, drug abuse, serious psychiatric diseases and cooperation issues. In addition, patients who had undergone abdominal surgery were excluded except for appendectomy, cesarean section and hysterectomy.

Six patients were regularly using one or a combination of several medications. Four patients consumed proton pump inhibitors (PPI), one used an antihypertensive (angiotensin II receptor antagonist), three patients used medications against allergies, two consumed contraceptive pills, two took thyroxin substitution tablets, one used an inhalator against asthma, and two used antidepressants/anxiolytics. These patients were informed not to take any kind of PPI during the study.

The control group consisted of patients with gastrointestinal bleeding, where the source of bleeding was identified as hemorrhoids (*n*=3) or angiodysplasia (*n*=1), or healthy subjects who underwent endoscopy due to health worries caused by family member(s) having been diagnosed with gastrointestinal cancer (*n*=10). The control group included 14 subjects (nine females and five males with a mean age of 54 years [range 26-70 years]) who underwent gastroscopy. One male of the control subjects with a familial history of gastrointestinal cancer did not consent to colonoscopy, therefore; only 13 control subjects (nine females and four males) underwent colonoscopy.

## 3.2 Study design

Forty-six patients were included in the study. This included 35 females and 11 males with a mean age of 35 years (range, 18-69 years). Of these, 21 reported diarrhea (IBS-D), 18 reported constipation (IBS-C) and seven reported a mixture of both symptoms (IBS-M) as the predominant symptom of IBS. The patients underwent a complete physical examination, a gastroscopy with duodenal biopsies (to exclude celiac disease), a colonoscopy with segmental biopsies (to exclude microscopic colitis) and several blood tests to exclude other organic causes for their symptoms. Each patient received three 45-min sessions of individualized dietary guidance with a registered nurse with a specific education in IBS diet, at intervals of at least 2 weeks. The patients were asked to complete the following questionnaires before and 3–9 months (median, 4 months) after receiving the last session of the dietary guidance: The Birmingham IBS symptom score questionnaire, the IBS-Quality of Life (IBS-QOL) questionnaire, the Norwegian version of the Short-Form Nepean and Dyspepsia Index (SF-NDI) questionnaire and the MoBa Food Frequency Questionnaire (MoBa FFQ). The patients also underwent a second gastroscopy and colonoscopy with new biopsy sampling 3–9 months (median, 4 months) after receiving the last session of dietary guidance.

## 3.3 Individualized dietary guidance

Dietary guidance was delivered orally with the help of charts and written illustrations. During the first session, the patients received general information about IBS. The patients were informed about the importance of keeping a regular and healthy eating pattern, and to avoid consuming food items rich in FODMAPs and insoluble dietary fibers that worsen IBS symptoms. During the study, the patients were supposed to test alternating diets that were rich in protein followed by protein-poor diet each for 2-3 days, then fat-rich/poor and carbohydrates-rich/poor diets in the same manner as for proteins. The patients were asked to register for 2 weeks in a diary the time and type

of food and fluids they consumed daily along with any associated symptoms, including the frequency and degree of abdominal pain and distension, and the stool frequency and consistency. The consumption of food supplements containing probiotics, antibiotics and other medications such as PPI was prohibited during the study.

In the second session, the information given during the first session was briefly repeated and the patients' diary was used to identify the food items that triggered IBS symptoms. Based on the obtained information, the patients were asked to alter their diet proportions of protein, fat and carbohydrates, and to consume vegetables and fruits that were low in FODMAPs and contained soluble fibers instead of foods rich in FODMAPs as well as insoluble fibers, Table 7.

During the third session, each patient gave his/her feedback about the dietary guidance to the nurse, and together with the nurse designed a suitable diet for the patient to follow until the end of the study.

Table 7. Examples of food items rich with FODMAPs (not allowed) and FODMAP-poor items (allowed).

FODMAP-rich (not allowed)	FODMAP-poor (allowed)	
Wheat	Spelt and spelt products	
Pasta	Meat	
Maize	Fish	
Mushrooms	Chicken	
Onion	Fat and oil	
Garlic	Rice	
Paprika	Potato	
Banana	Carrots	
Beans	Beans Apples and pears (peeled)	
Peas	Citrus fruits	

Table 7. (Continued)			
FODMAPs-rich (not allowed)	FODMAPs-poor (allowed)		
Grapes	Tomato		
Cauliflower	Lactose-free milk		
Broccoli	Lactose-free dairy products		
Carbonated drinks	Coffee and tea		
Artificial sweeteners	Chocolate		
	Alcohol		

Table 7 (Continued)

# 3.4 Assessments and investigations

#### 3.4.1 Questionnaires

#### 3.4.1.1 The Birmingham IBS symptom score questionnaire

This questionnaire was developed for assessing the symptoms of IBS patients. The dimensions of the questionnaires are reliable, sensitive, and with good external validity (220). The questionnaire consists of 11 questions focusing on 3 domains: pain (3 items), diarrhea (5 items) and constipation (3 items), and the responses to the questions are measured on a six-point Likert scale, ranging from 0 (none of the time) to 5 (all of the time) (Appendix I). Lower scores indicate improved symptoms.

## 3.4.1.2 The IBS-Quality of Life (IBS-QOL) questionnaire

This 34-item questionnaire, which is validated in IBS, measures specifically the quality of life of IBS patients by assessing physical and psychosocial functioning as a result of IBS (221, 222). It comprises eight domains; dysphoria, interference with activity, body image, health concerns, food avoidance, social reaction, sexual function and impact on relations. The following five-point Likert scale is used in the questionnaire's responses: not at all, slightly, moderately, quite a lot and extremely

(Appendix II). Lower scores indicate reduction in the quality of life related to these domains.

# 3.4.1.3 The Norwegian version of the Short-Form Nepean Dyspepsia Index (SF-NDI) questionnaire

The questionnaire consists of five subscales scores with two items each, and is a disease-specific measure of the health-related quality of life (HRQoL). The five subscales are: tension, interference with daily activities, disruption to regular eating/drinking, knowledge towards/control over disease symptoms and interference with work/study. The answer to each question consists of five options, ranging from 1 (not at all) to 5 (extremely); and the total score ranges from 10-50. Higher scores indicate worse functioning or symptoms (quality of life). This questionnaire was constructed and validated originally for patients with dyspepsia (223). A Norwegian translation of the questionnaire was validated for patients with IBS (224) (Appendix III).

## 3.4.1.4 The MoBa Food Frequency Questionnaire (MoBa FFQ)

A semi-quantitative, self-administered questionnaire used to assess dietary intake. The MoBa FFQ reports the frequency of consumption of line items (225 food items/ beverages, grouped according to typical Norwegian meal patterns) and their portion size over a defined period of time. It is designed to capture the dietary habits and the meal patterns of the participant. The analysis of the questions is done using software for nutrient calculations. This questionnaire was developed and validated by the Norwegian Institute of Public Health in Oslo, Norway (225, 226) (Appendix IV).

# 3.4.2 Tissue sampling

Following an overnight fast and bowel preparation, both the patients and controls were examined with gastroscopies with biopsy samples taken from the corpus and the antrum of the stomach, and colonoscopies with biopsy samples taken from each

segment of the colon and the rectum. These investigations were performed before the first session and at 3–9 months (median, 4 months) following the third session of dietary guidance.

## 3.4.3 Histopathology and immunohistochemistry

The biopsy samples were fixed in 4% buffered paraformaldehyde overnight, embedded in paraffin wax, and then were cut into 5-µm sections. Biopsy samples from the stomach and duodenum underwent histopathological examinations. Biopsy samples from the stomach (paper II and III) and large intestine (paper IV and V) were stained with hematoxylin and eosin and immunostained with the avidin-biotin complex method using a Vectastain ABC kit (Vector laboratories, Burlingame, CA, USA) and the chromogen 3,3'-diaminobenzidine peroxidase substrate (DAB) kit (Vector Laboratories) as described in the papers.

## 3.4.4 Computerized image analysis

The density of the different endocrine cells in the stomach and large intestine in patients with IBS and controls were measured using Olympus Cell^D software, Olympus, (Tokyo, Japan). The number of immunoreactive positive cells and the area of the epithelial cells were measured in 10 randomly selected fields, using the magnification x40. At this magnification each field represented a tissue area of 0.14 mm<sup>2</sup>. The cell density was expressed as the number of cells/mm<sup>2</sup> of the epithelium. The quantifications were performed by one and same person (Tarek Mazzawi), who was blinded to the identity of the sections. Computer image analysis was used for quantifying endocrine cells and for studying the changes in the number of endocrine cells (227).

## 3.5 Ethics

All studies were performed according to the Declaration of Helsinki and were approved by local ethics committees. Oral and written consents to participate in the studies were obtained from the patients.

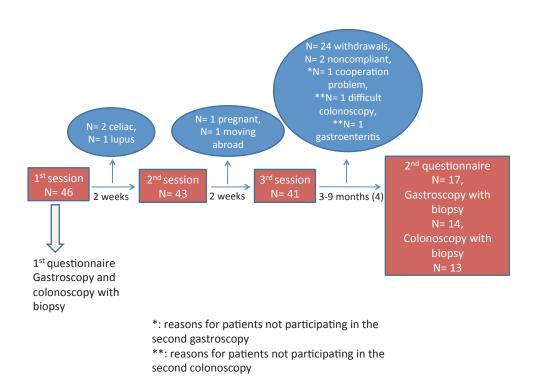
# 3.6 Statistical analysis

The paired t-test was used to analyze the data of the patients before and after receiving dietary guidance and the unpaired t-test was used to analyze the data of the patients who fulfilled the entire study and those who did not. The data are presented as the mean  $\pm$  standard error of mean (SEM). P<0.05 was considered to indicate a statistically significant difference.

# 4. RESULTS

Forty-six patients were included in the study; some did not complete the entire study and withdrew their consents or were excluded at different stages of the study due to different reasons, as shown in the flow chart, Fig. 4.

Figure 4. Flow chart of the patients during the study.



# 4.1 Paper I

Seventeen patients (12 females and five males, mean age of 34 years; range, 20-45 years) completed the four questionnaires before and 3-9 months (median 4 months) after dietary guidance:

- 1) Birmingham IBS symptom score questionnaire. The total scores of the Birmingham IBS symptom score questionnaires before and 3-9 months after receiving dietary guidance were significantly reduced from  $41.47\pm1.62$  and  $35.71\pm1.12$ , respectively, (P=0.001). The questionnaire's dimensions; abdominal pain and diarrhea were also significantly reduced following dietary guidance (P=0.003, 0.018, respectively), however, the reduction for constipation was not statistically significant (P=0.06). By comparing the Birmingham's total-, abdominal pain-, diarrhea-, and constipation-scores between the patients who fulfilled the entire study and those who did not, we found that there were not significant differences between them (P=0.9, 0.5, 0.5, 0.9, respectively).
- 2) *IBS-QOL*. The total IBS-QOL score increased significantly from 125.4 $\pm$ 4.2 to 136.8 $\pm$ 3.8 following dietary guidance (P=0.003). This improvement was statistically significant in all domains, with the exception of the impact on relations. There was no significant difference between the patients who completed the entire study and those who did not (P=0.3).
- 3) *SF-NDI*. The total SF-NDI scores (which reflect the reduction in health related quality of life (HRQoL)) before and following dietary guidance were 29.1 $\pm$ 2.2 and 20.2 $\pm$ 1.5, respectively. This improvement in HRQoL was statistically significant (P=0.002). No significant difference was found between the patients who completed the entire study and those who did not (P=0.4).
- 4) *MoBa FFQ*. The dietary guidance did not affect the meal pattern in the patients with IBS. There were no statistically significant differences in the intake of calories,

carbohydrate (total and starch), fiber, protein, fat (total, saturated and trans-, monoand polyunsaturated), sugar or alcohol in the patients with IBS who received dietary guidance. There was a statistically insignificant increase in the consumption of various dairy products, but the consumption of dairy products with probiotic supplements was reduced, which is in line with our recommendation during the study. Although the intakes of  $\beta$ -carotene, retinol equivalents, calcium and riboflavin were increased, only the increase in vitamin B12 was statistically significant. A significant reduction was noted in the daily total consumption of fruits and vegetables rich in FODMAPs from 16.2±5.3 g before receiving dietary guidance to 9.2±3.2 g after receiving dietary guidance (P= 0.02). However, no significant difference was found in the daily consumption of fiber before receiving dietary guidance (27.4±2.5 g) compared to after receiving dietary guidance (23.1±2.2 g, P=0.09).

## 4.2 Paper II

Only 14 patients completed the study and underwent a second gastroscopy as illustrated in Fig. 4. They were nine females and five males with a mean age of 34 years (range, 20-45 years). The esophagus, stomach and duodenum had normal macroscopic and microscopic findings. CgA immunoreactive cells were identified in the mucosa of the stomach in both groups. An immunoreactive endocrine cell was either basket-or flask-shaped with/without a long basal cytoplasmic process, Fig. 5. The densities of the CgA-immunoreactive cells in the corpus in patients with IBS prior to and following dietary guidance were increased significantly (*P*=0.0064), however, there was no significant increase in the densities of CgA-immunoreactive cells in the antrum of these patients (*P*=0.2), Table 8.

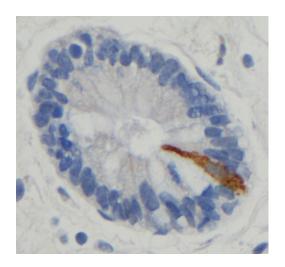


Figure 5. A flask-shaped intestinal PYY immunoreactive cell (brown color). Note that the cell extended in the crypt to the gut lumen.

# 4.3 Paper III

Of the 46 patients included in the study only 14 patients (nine females and five males with a mean age of 34 years; range, 20-45 years) completed the study and underwent a second gastroscopy as illustrated in the flow chart, Fig. 4.

Upper endoscopy of the esophagus, stomach and duodenum revealed a normal appearance, and histopathological examinations of these structures were normal. Ghrelin-positive cells were found only in the oxyntic mucosa of the corpus, and gastrin-positive cells were found exclusively in the antrum, whereas serotonin- and somatostatin-immunoreactive cells were found in the mucosa of both the corpus and antrum in the patients and controls. The number of histamine immunoreactive cells in the biopsy samples used in the study was low and did not allow reliable quantification. The quantification of gastric endocrine cells showed that only somatostatin immunoreactive cells in the corpus in IBS patients increased significantly after receiving dietary guidance (P = 0.02). The rest of the gastric endocrine cell densities are shown in Table 8.

Table 8. Densities of immunoreactive endocrine cells in the corpus and antrum in the stomach of control subjects and of IBS patients before and after receiving dietary guidance.

Endocrine cell densities (cells/mm <sup>2</sup> )				
Hormone	Control	Before	After	<i>P</i> -value
(location)		guidance	guidance	
Chromogranin A	147.9±15.8	62.6±9	102.0±14.0	$0.006^{b}$
(corpus)				
Chromogranin A	87.7±20.3	28.5±6.5	46.5±11.0	0.2
(antrum)				
Ghrelin (corpus)	149.6±36.2	114.5±32.7	161.8±37.8	0.09
Gastrin (antrum)	155.8±21.0	159.4±24.3	211.6±28	0.26
Serotonin	18.2±3.9	10.6±3.4	$14.0\pm2.0$	0.4
(corpus)				
Serotonin	44.6±12.2	1.7±0.5	14.7±6.3	0.06
(antrum)				
Somatostatin	40±7.7	23±3	37.3±4.2	$0.02^{a}$
(corpus)				
Somatostatin	138.9±22	95.6±15.9	86±16.9	0.6
(antrum)				

Data are presented as the mean $\pm$ SEM. a: P < 0.05, b: P < 0.01

## 4.4 Paper IV

Of the 46 patients recruited in the study, only 13 patients completed the study and underwent a second colonoscopy; these patients comprised 8 females and 5 males with a mean age of 34 years (range 20–45 years) as illustrated in the flow chart, Fig. 4.

The colon and rectum were macroscopically normal and the histopathological examinations revealed normal structures in both patients and controls. CgA-immunoreactive cells were found in the mucosa of both the colon and rectum of the patients and controls.

The densities of CgA cells in the total, right and left colon of IBS patients were statistically significantly increased after receiving dietary guidance (P=0.0032, 0.0157 and 0.0039, respectively) as shown in Table 9. However, the cell density in the rectum did not differ significantly before and after receiving dietary guidance in the IBS patients (P=0.47), Table 10.

# 4.5 Paper V

Thirteen of the original 46 patients completed the study, comprising 8 females and 5 males with a mean age of 34 years (range 20–45 years) and underwent a second colonoscopy, as illustrated in the flow chart, Fig. 4. The colonoscopies indicated that the colon and rectum were normal both macroscopically and microscopically in both patients and controls. Immunoreactive endocrine cells were found in the mucosa of both the colon and rectum of the patients and controls. The numbers of pancreatic polypeptide- and, oxyntomodulin (enteroglucagon)-immunoreactive cells in the biopsy samples of the colon and rectum used in the study were too low to allow reliable quantification. There were also too few somatostatin cells in the colon to allow reliable quantification.

The density of serotonin cells in the total colon and the right colon of IBS patients increased significantly (P=0.007 and P<0.0001, respectively) after receiving dietary guidance. The density of serotonin cells in the left colon also increased after receiving dietary guidance, but this increase was not statistically significant (P= 0.53). The endocrine cell densities in the colon in the control subjects and patients are shown in Table 9.

The densities of PYY cells in the controls and patients are summarized in Table 9. The density of PYY cells of IBS patients increased significantly (P=0.04) in the left colon but did not increase significantly in the total colon and the right colon (P= 0.06 and P= 0.1, respectively) after receiving dietary guidance.

In the rectum, the densities of serotonin, PYY and somatostatin cells in controls and patients are reported in Table 10. The densities of PYY- and serotonin-immunoreactive cells in the rectum of IBS patients did not change significantly (P=0.13 and P=0.06, respectively) after receiving dietary guidance. However, the somatostatin cell density of IBS patients increased significantly (P=0.01) after receiving dietary guidance.

Table 9. The densities of chromogranin A-, serotonin- and PYY-immunoreactive cells in the total colon, right colon, and left colon in control subjects and in IBS patients before and after receiving dietary guidance.

Endocrine cell densities (cells/mm <sup>2</sup> )				
Hormone/location	Control	Before guidance	After guidance	P-value
Chromogranin A				
Total colon	83.3±10.1	38.6±3.7	64.7±4.2	$0.0004^{b}$
Right colon	33.7±5.3	16.7±1.9	24.4±2.1	$0.0157^{b}$
Left colon	$49.6 \pm 6.0$	21.9±2.7	40.3±3.6	$0.0039^{b}$
Serotonin				
Total colon	$46.8 \pm 8.9$	10.5±2.1	22.6±3.2	$0.007^{b}$
Right colon	25.9±5.4	$1.2 \pm 0.8$	10.7±1.6	<0.0001°
Left colon	$20.9 \pm 4.8$	$8.9 \pm 1.7$	10.6±1.9	0.53
PYY				
Total colon	11.6±1.8	10.8±1.7	$16.8 \pm 2.1$	0.06
Right colon	$3.9 \pm 0.8$	$2.9 \pm 0.8$	5.5±1.1	0.1
Left colon	7.7±1.4	7.9±1.0	11.5±1.1	$0.04^{a}$

Data are presented as the mean $\pm$ SEM. a P<0.05, b P<0.01 and c P<0.0001.

Table 10. Densities of chromogranin A, serotonin-, PYY-, and somatostatin-immunoreactive cells in the rectum of control subjects and of IBS patients before and after receiving dietary guidance.

	Endocrine cell densities (cells/mm <sup>2</sup> )			
Hormone	Control	Before guidance	After guidance	<i>P</i> -value
Chromogranin A	49.0±7.9	42.7±6.5	47.6±5.0	0.47
Serotonin	37.7±10.5	$31.9 \pm 6.4$	$19.6 \pm 4.5$	0.06
PYY	32.5±5.1	$38.4 \pm 5.0$	31.5±3.7	0.13
Somatostatin	13.5±3.0	13.2±3.0	22.3±3.2	$0.01^{a}$
Data are presented as the mean±SEM. a <i>P</i> <0.05.				

## 5. GENERAL DISCUSSION

#### 5.1 Patients

There was no significant difference regarding age (P=0.8), gender (P=0.7), symptoms and quality of life (see Results section) between the patients who completed the whole study and those who did not. This means that the results obtained from the remaining small sample are non-selective and representative of the entire group of patients who were originally included.

#### 5.2 Diet

Diet is considered to be one of the important factors for the development of IBS symptoms as the majority of the patients relate their symptoms to certain foods (61, 80, 81), so choosing the right kind of food is important for reducing these symptoms (84). FODMAPs have positive effects on the colonic microbiota, therefore, colonic health (228-230). Butyrate, a short chain fatty acid and a product of colonic bacterial fermentation of carbohydrates, is the major energy element for colonic epithelium (231, 232), also a regulator of colonocyte proliferation and apoptosis and has an immunomodulatory effect (228, 233). Thus, fermentable carbohydrates in the colon have potential anti-carcinogenic and anti-inflammatory effects (228, 234). The FODMAP-poor diet is proven to be efficient in reducing IBS symptoms (24, 83, 125, 128, 235). The problem with this kind of diet resides in following it for a long time without previously receiving proper guidance, which can cause health problems, for example lack of nutrients (24) (especially calcium (127)) and reduction of luminal bifidobacteria (127) and fecal microbiota (228). Therefore, avoiding such adverse effects of long-term usage of a FODMAP-poor diet requires the administration of dietary guidance (83).

# 5.3 Dietary guidance

Due to the impact of IBS on the patients' health and economy, educating patients facilitate changes in their behavior for the purpose of disease management and prevention (87). The lack of evidence-based guidelines for dietary management of IBS in practice (84, 236) is probably the reason for the absence of an effective educational model for IBS patients (87). However, guidance has been recently developed for improving the dietary approach available (114, 237). The patients are mainly interested in learning about dietary modifications, coping strategies and the causes of IBS (87). In the individual dietary guidance given during this study, information was delivered orally as well as written illustrations. Patients often tend to select parts of any diet that appeal to them and ignore the rest, which could compromise the ability of using only written information to achieve efficacy (83). Therefore, caution must be practiced by clinicians when using such an approach as the ability of using written information only to achieve efficacy has not been studied (83).

The patients received individual dietary guidance and were instructed to try food rich/poor in proteins, fat and carbohydrates and were provided with a list showing some of the foods containing lower FODMAPs they could use in exchange for item rich in FODMAPs, Table 7. This mild dietary restriction did not include all the food items that were rich in FODMAPs with the purpose of providing the patients with dietary instructions that they could adhere to in the future. The patients were asked to register their symptoms in a diary. After reviewing the diaries, we noticed that the symptoms of the patients improved after they reduced their consumption of FODMAP-rich products (P= 0.02), Table 11. In spite of the alternating types of diet composition (protein-, fat-, carbohydrates- rich/poor diets), the patients favored using a FODMAP-poor diet primarily to reduce their IBS symptoms, which is in line with previous studies (24, 83, 125, 235).

Table 11. FODMAPs consumed by the patients before and after receiving dietary guidance.

FODMAP-rich items	Before guidance	After guidance
Artificial sweeteners (mg)	0.02	0.01
Soft drinks (sweetened) (ml)	71.3	53.5
Soft drinks (unsweetened) (ml)	91.7	37.5
Dark bread (g)	85.4	48
White bread (g)	3.4	4.4
Pasta (g)	15.1	13.4
Onion, leak or garlic (g)	11.5	1.7
Paprika (raw) (g)	4.9	1.8
Paprika (cooked) (g)	3.3	0.7
Cabbage (raw) (g)	1.5	0.1
Cabbage (cooked) (g)	2.3	0.2
Cauliflower (raw) (g)	1.4	0.7
Cauliflower (cooked) (g)	4.9	4.9
Broccoli (raw) (g)	1.5	1.2
Broccoli (cooked) (g)	5.2	5.4
Banana (g)	24.1	4.7
Beans (g)	0.3	0.3
Peas (g)	2.1	0.4
Grapes (g)	16.2	2.6
Pears (g)	16.5	4.5
Apples (g)	29.3	34.7
Peaches (g)	8.9	6.7
Grapefruit (g)	1.4	0.6
Mushrooms (g)	1.7	1.4
Green beans (g)	0.3	0.3

The patients were advised to replace wheat with spelt and spelt products. Spelt is low in FODMAPs, contains less galactans and fructans than wheat (89) and thus allows the patients to continue consuming food items, such as bread and pasta. In addition, the patients were allowed to consume rice, which is also low in FODMAPs (89), and is completely absorbed in the small intestine thus producing little amount of intestinal gas and is well tolerated by patients with functional GI disorders (238). This could explain why there was not a significant decrease in the consumption of total carbohydrates and rather a significant decrease in FODMAPs after receiving dietary guidance. Furthermore, the patients were told to consume lactose-free milk and lactose-free dairy products that are major sources of calcium and to avoid products containing lactose (82, 83, 122, 236). As a result, three 45-min sessions of dietary guidance provided by a nurse, improved the symptoms and the quality of life of patients with IBS, and improved their vitamin and mineral intake. This indicates that dietary guidance is important in the treatment of IBS.

#### 5.4 Diet and endocrine cells

Despite the fact that delivering dietary FODMAPs to the distal small intestine and proximal colon is physiologically normal, it generates symptoms if the underlying bowel response is exaggerated or abnormal (83). The endocrine cells of the gut are part of the ENS and are found to be abnormal in IBS patients (3, 52, 136, 170, 197-204, 207-209, 239-246). Such abnormalities may explain the abnormal functions in the GI tract in IBS patients namely; visceral hypersensitivity, dysmotility and abnormal secretion (52, 247-249).

CgA is a common marker for the endocrine cells of the gut and is proposed as a biomarker for diagnosis of IBS (170, 239). The densities of CgA immunoreactive cells, representing the total endocrine cells, were abnormal in the gastric corpus and antrum as well as in the colon, but not the rectum, in IBS patients before receiving dietary guidance, which is in accordance with previous studies (170, 201, 241). However, after receiving dietary guidance, the densities of CgA immunoreactive cells

in the stomach and the colon, except for the rectum, changed towards the values of healthy controls. The specific endocrine cell types that have changed towards the values of healthy controls following dietary guidance were gastrin, ghrelin, serotonin and somatostatin cells in the stomach, and serotonin and PYY in the colon.

Considering the effect of the hormones secreted by these cells, it is conceivable to conclude that changes in these cells towards normal levels following dietary guidance may contribute to improvements in IBS symptoms associated with disturbed gut motility, visceral hypersensitivity and abnormal gastrointestinal secretion. As for the rectum, such changes did not occur. This is most probably due to fact that the rectum acts only as a fecal reservoir prior to defecation (201) and is not involved in the functions disturbed in IBS patients.

The endocrine cells of the gut play a major role in the regulation of the GI functions and are important players in the pathogenesis of IBS (13, 52, 67, 170, 250, 251). These cells exert their effects through microvilli that extend into the gut lumen to sense the gut's luminal contents, especially nutrients, and respond by releasing specific gut hormones (34, 135, 136, 153-163). The endocrine cells originate from 4-6 pluripotent stem cells in each intestinal crypt. The stem cells differentiate through a series of cellular precursors (progenitors) into all the epithelial cells including endocrine cells (252-261). This differentiation is rapid (approximately 2-4 days) (151, 152). A change in diet may affect the differentiation of stem cells into endocrine cells in a way similar to that in healthy subjects. The observation that dietary guidance can restore the density of endocrine cells in IBS patients to approach the level of healthy subjects, suggests that these changes may be one of the causes for the reduction of IBS symptoms and the improvement in the quality of life of these patients.

## 6. LIMITATIONS

The main limitation of this study is the low number of the patient cohort studied and the hazard of selecting a sample of patients that does not present the IBS patient population. Clinical studies involving IBS patients are known to suffer a high drop out rate ranging from 33% to 48% (24, 125, 262-264). In this study, 72% of the patient did not complete the entire study. This could be mostly explained by the demanding design of the study, which required adherence to a strict diet for at least 3 months and included a total of four endoscopic examinations (two gastroscopies and two colonoscopies). Of this high percentage, 52% of the patients withdrew their consent to participate due to symptom improvement following dietary guidance, non-compliance or unwillingness to go through four endoscopic examinations. The remaining 20% were excluded after being diagnosed with celiac disease or lupus, becoming pregnant, moving abroad and technical difficulties experienced during some endoscopies. There was no significant difference between the patients who completed the study and those who did not regarding age, gender, symptoms, and quality of life. Thus, a bias sample selection is highly improbable.

## 7. CONCLUSION AND FURTHER PERSPECTIVES

Individual dietary guidance reduced the symptoms of IBS patients and improved their quality of life. This improvement was accompanied by changes in the densities of the gastrointestinal endocrine cells to normal levels. Regardless of the small sample size, we showed, for the first time, a clear effect of individual dietary guidance on the densities of the endocrine cells in the stomach and the large intestine in IBS patients.

These results strengthen the practice of using dietary guidance in the management of IBS as a first line treatment (84). In addition, the results support that the endocrine cells of the gut are major players in the pathogenesis of IBS. The interactions between these cells and specific types of food result in changing their densities, which either worsen or alleviate IBS symptoms. Further studies on a larger cohort of IBS patients are needed. Moreover the effect of dietary guidance on the small intestinal endocrine cells remains to be determined.

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#### 9. APPENDIX I-IV

**Appendix I** The Birmingham IBS symptom score questionnaire

**Appendix II** The IBS-Quality of Life (IBS-QOL) questionnaire

**Appendix III** The Norwegian version of the Short-Form Nepean Dyspepsia

Index (SF-NDI) questionnaire

**Appendix IV** The MoBa Food Frequency Questionnaire (MoBa FFQ)

## Appendix I The Birmingham IBS symptom score questionnaire

		Hele tida	Det meste av tida	Ein heil del av tida	Av og til	Ein liten del av tida	Ikkje i det heile tatt
1.	Kor ofte har du ubehag eller smerte i magen?						
2.	Kor ofte har du problem med laus, eller vatn tynn avføring?						
3.	Kor ofte har du problem med diaré?						
4.	Kor ofte har du hard avføring?						
5.	Kor ofte har du behov for å presse, for å få ut avføring?						
6.	Kor ofte har du problem med forstoppelse?						
7.	Kor ofte har du ubehag eller smerte etter at du har spist?						
8.	Kor ofte har du vanskar med å sove eller har du våknet på grunn av magesmerte?						
9.	Kor ofte har du problem med å halde på avføring?						
10.	Kor ofte må du springe til toalettet fordi det er vanskelig å halde seg?						
11.	Kor ofte har du slim i avføringen?						

### Appendix II The IBS-Quality of Life (IBS-QOL) questionnaire

#### IBS-QOL- helse undersøking

Ve	er venleg og svar på a	lle spørsmål. Nokre spørsmål	verkar like, men dei er ulike
Na	nvn	persnr.	Dato
1.	Eg kjenner meg h	jelpelaus på grunn av mage	eplagene mine:
	Aldri		
	Av og til		
	Ofte		
	Svært ofte		
	Alltid		
2.	Eg føler at lukta s	om kjem av tarmproblema	mine plagar meg:
	Aldri		
	Av og til		
	Ofte		
	Svært ofte		
	Alltid		
3.	Eg synest eg bruk	ar for mykje tid på toalette	t:
	Aldri		
	Av og til		
	Ofte		
	Svært ofte		
	Alltid		

4.	Eg føler eg har lett for å bli sjuk på grunn av magetarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
5.	Eg kjenner meg oppblåst på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
6.	Eg føler eg ikkje har kontroll over livet mitt på grunn av tarmproblema:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

7.	Eg føler livskvaliteten er nedsatt på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
8.	Eg føler det ubehageleg å snakke om tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
9.	Eg føler meg deprimert på grunn av tarmproblema mine:
9. <b>□</b>	Eg føler meg deprimert på grunn av tarmproblema mine: Aldri
	Aldri
_ _	Aldri Av og til
_ _	Aldri Av og til Ofte
	Aldri Av og til Ofte Svært ofte
	Aldri Av og til Ofte Svært ofte
	Aldri Av og til Ofte Svært ofte Alltid
10	Aldri Av og til Ofte Svært ofte Alltid  Eg føler meg isolert frå andre på grunn av tarmproblema mine:
10	Aldri Av og til Ofte Svært ofte Alltid  Eg føler meg isolert frå andre på grunn av tarmproblema mine: Aldri
10	Aldri Av og til Ofte Svært ofte Alltid  Eg føler meg isolert frå andre på grunn av tarmproblema mine: Aldri Av og til

11.	Eg må ta hensyn til mykje av maten eg et på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
12.	Seksuell aktivitet er vanskeleg for meg på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
13.	Eg er sint fordi eg har tarmproblem:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
14.	Eg føler at eg irriterer andre på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

15.	Eg er redd for at tarmproblema mine skal bli verre:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
16.	Eg er irritert på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
17.	Eg er redd for at andre synest eg overdriv tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
18.	Eg føler at eg gjer lite på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

19.	Eg må unngå stress-situasjonar på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
20.	Tarmproblema mine reduserer min seksuelle lyst:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
21. <b>N</b>	Iine klesval blir begrensa på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
22.	Eg må unngå tunge aktivitetar på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

23.	Eg må vera nøyen med kva eg et på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
24.	På grunn av tarmproblema mine, er det vanskeleg for meg å vera med andre
som	eg ikkje kjenner godt:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
25.	Eg kjenner meg trøytt på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
26.	Eg føler meg urein på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

27.	Eg kan ikkje ta lange turar eller lange reiser på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
28.	Eg er frustrert over at eg ikkje kan eta kva eg vil på grunn av tarmproblema
min	ne:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
29.	Det er viktig å vera i nærleiken av toalett på grunn av tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
30.	Livet mitt er sentrert om tarmproblema mine:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid

31.	Eg er redd for å miste kontroll over tarmen min:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
32.	Eg er redd for at eg ikkje vil kunna tømma tarmen min:
	Aldri
	Av og til
	Ofte
	Svært ofte
	Alltid
33.	Tarmproblema mine påverker mine næraste forhold:
33. <b>□</b>	Tarmproblema mine påverker mine næraste forhold:
	-
	Aldri Av og til
<u> </u>	Aldri Av og til Ofte
	Aldri Av og til Ofte
	Aldri Av og til Ofte Svært ofte
	Aldri Av og til Ofte Svært ofte
	Aldri Av og til Ofte Svært ofte Alltid
34.	Aldri Av og til Ofte Svært ofte Alltid  Eg føler at ingen forstår seg på tarmproblema mine:
34.1	Aldri Av og til Ofte Svært ofte Alltid  Eg føler at ingen forstår seg på tarmproblema mine: Aldri
34.1	Aldri Av og til Ofte Svært ofte Alltid  Eg føler at ingen forstår seg på tarmproblema mine: Aldri Av og til Ofte

# Appendix III The Norwegian version of the Short-Form Nepean Dyspepsia Index (SF-NDI) questionnaire

#### SF-NDI (Spørreskjema om livskvalitet) (sett kryss ved ett tall)

#### **Spenning**

1. Har ditt følelsesmessige velvære	e vært forstyrret av d	ine mageplager i løp	et av de siste
to ukene?			

- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye
- 2. Har du vært irritabel, anspent eller frustrert på grunn av dine mageplager i løpet av de siste to ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye

#### Innflytelse på daglige aktiviteter

- 3. Har din evne til å holde på med fritidsaktiviteter (rekreasjon, hobbyer, idrett, sosialt samvær osv.) vært forstyrret av dine mageplager i løpet av de siste to ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye
- 4. Har gleden ved dine fritidsaktiviteter (rekreasjon, hobbyer, idrett, sosialt samvær osv.) vært forstyrret av dine mageplager i løpet av de siste to ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye

#### Spising/drikkig

- 5. Har mageplagene dine forstyrret deg i hva du har kunnet spise og drikke (inkludert når, hva og hvor mye) i løpet av de to siste ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del

- 4 p ganske mye
- 5 p svært mye
- 6. Har din mulighet til å nyte mat og drikke vært forstyrret på grunn av dine mageplager i løpet av de to siste ukene? (Vennligst ta i betraktning din matlyst og hvordan du føler deg etter at du har spist eller drukket.)
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye

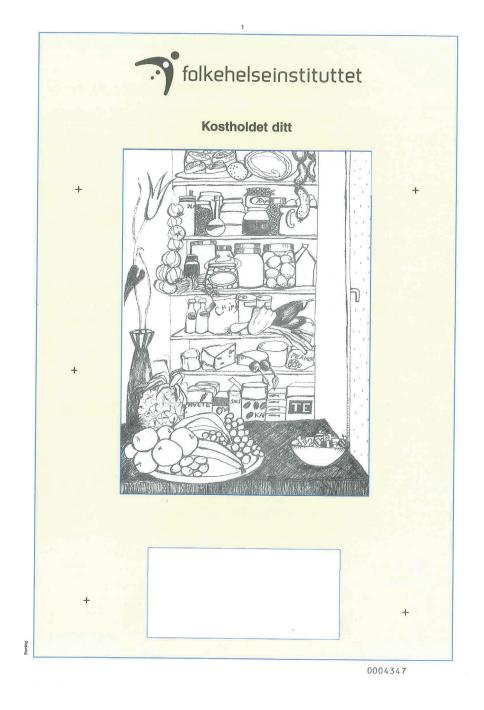
#### Kunnskap/kontroll

- 7. Har du, i løpet av de to siste ukene, lurt på om du alltid kommer til å ha disse mageplagene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye
- 8. Har du, i løpet av de to siste ukene, lurt på om mageproblemene dine kan skyldes en svært alvorlig sykdom (for eksempel kreft eller hjerteproblemer)?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye

#### Arbeid/studier

- 9. Har din evne til å arbeide eller studere vært forstyrret av dine mageplager i løpet av de siste to ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye
- 10. Har mageproblemene dine forstyrret trivselen i ditt arbeide eller i dine studier i løpet av de to siste ukene?
- 1 p ikke i det hele tatt
- 2 p litt
- 3 p en del
- 4 p ganske mye
- 5 p svært mye

## Appendix IV The MoBa Food Frequency Questionnaire (MoBa FFQ)



+ Veiledning for utfylling av kostskjemaet

Vi	takker for at du vil hjelpe oss	med d	denne	e und	ersøk	elser	).							
er	ijemaet skal leses av en ma	ekin /	Dot o	r dar	for v	iktica	at du	loggo	, vok	nå fo	laand	0 1/00	1 ,,06,	llingor
9	Bruk blå eller sort kulepenn.	okiii. I	001 0	i dei	101 0	intig	at uu	legger	VER	pano	igena	e vec	ully	illigen
	I de små avkrysningsboksene setter	du et k	ryss fo	or det s	svaret	som di	mene	passer	best, s	slik: X				
D	Du skal sette ett kryss på hver linje.													
D	Skriver du feil, kan du ta bort krysse	et ved å	fylle b	oksen	helt, s	lik:	og dere	etter fylle	i det r	iktige al	ternativ	et.		
	Eksempel:													
	Encompon					Anta	ll brøds	kiver me						
	Ost	6+	5	pr.	dag 3	2	1	ell 5-6	er pr. u 3-4	1-2	3	ller pr. 2	måned 1	0
	Oat	01	U	-	U	-								U
)	Brunost (Gudbrandsdalsost o.l.)  Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten <u>Eksempel:</u> Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen for 2 ganger per mår	ike på h mm til n It spist ti	va du niddag orsk o	har sp	ist det	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø	nsnitt.	ve året,	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten <u>Eksempel:</u> Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen for 2 ganger per mån	ike på h mm til n It spist ti	va du niddag orsk o	har sp i 1 gan g sei 2	6+ bety ist det g i uke 4 gang pr. uke	siste å en i 6 n ger. I gj	ret og a	angi et g r på rad, snitt blir	jennon det fø dette 2	nsnitt.	ve året, v	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten <u>Eksempel:</u> Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen for 2 ganger per mån  Middag med fjerfe	ike på h mm til n It spist ti	va du niddag orsk o	har sp 1 gan g sei 2	6+ bety ist det g i uke 4 gang	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø dette 2	nsnitt. rste halv ganger	ve året,	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten <u>Eksempel:</u> Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen for 2 ganger per mån	ike på h mm til n It spist ti	va du niddag orsk o	har sp i 1 gan g sei 2	6+ bety ist det g i uke 4 gang pr. uke	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø dette 2	nsnitt. rste halv ganger	ve året, v	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten <u>Eksempel:</u> Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen for 2 ganger per mån  Middag med fjerfe	ike på h mm til n It spist ti	va du niddag orsk o	har sp i 1 gan g sei 2	6+ bety ist det g i uke 4 gang pr. uke	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø dette 2	nsnitt. rste halv ganger	ve året, v	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten Eksempel: Hvis du spiste torsk, sei i sei med mer etter dette, har du total kryss i boksen for 2 ganger per mån  Middag med fjerfe Grillet kylling  Enkelte steder kan du skrive tekst — Skriv tydelig	ike på h mm til n It spist ti ned slik;	va du niddag crsk o	har sp i 1 gan g sei 2	6+ bety ist det g i uke 4 gang pr. uke	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø dette 2 eller pr. 2	nsnitt. rste halv ganger	ve året, v	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten Eksempel: Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen lor 2 ganger per mår  Middag med fjørfe Grillet kylling Enkelte steder kan du skrive tekst	ike på h mm til n It spist ti ned slik;	va du niddag crsk o	har sp i 1 gan g sei 2	6+ bety ist det g i uke 4 gang pr. uke	siste å en i 6 n ger. I gj	iret og a nånede iennom	angi et g r på rad, snitt blir	jennon det fø dette 2 eller pr. 2	nsnitt. rste halv ganger	ve året, v	men ik	ke har	
	Hvor det står et + betyr dette "og flet Når du fyller ut skjemaet skal du ten Eksempel: Hvis du spiste torsk, sei sei med mer etter dette, har du total kryss i boksen lor 2 ganger per mån  Middag med fjerfe Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir t	ike på h mm til n It spist ti ned slik;	va du niddag orsk o	har sp i 1 gan g sei 2	6+ bety ist det ig i uke 4 gang pr. uke 3	siste å en i 6 n ger. I gj Antall 2	aret og a nånede. iennom middag 1	angi et g r på rad, snitt blir	jennon det før dette 2	nsnitt. rste halv ganger . måned 1	ve året, r r per må	men ik	kke hari	
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	va du niddag crsk o	har sp 1 1 gan g sei 2 4	ist det g i uke 44 gang pr. uke 3	siste å en i 6 n ger. I gj  Antall 2	iret og a nånede. iennom middag 1	angi et g r på rad, snitt blir	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	va du niddag crsk o	har sp 1 1 gan g sei 2 4	ist det g i uke 44 gang pr. uke 3	siste å en i 6 n ger. I gj  Antall 2	iret og a nånede. iennom middag 1	angi et g r på rad, snitt blir	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	5+	har sp 1 1 gam 1 g sei 2 4 4	pr. uke 3	siste å å fan i 6 n n	i om a svark	angi et g r på rad, snitt blir eer 3 3 + at du s	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	5+	har sp 1 1 gan 1 1 gan 2 g sei 2 4 1	pr. uke 3	siste å å an i 6 n n i	i om a svark	angi et g r på rad, snitt blir eer 3 3 + at du s convolu	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	5+	har sp 1 1 gan 1 1 gan 2 g sei 2 4 1	ist bety ist det g i uke 4 gang pr. uke 3	Antall  2  ber v  certe  miljø  kehels  404 N	i om a svark	angi et g r på rad, snitt blir eer 3 3 + at du s convolu	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	etter da
	Hvor det står et + betyr dette "og fle  Når du fyller ut skjemaet skal du ten  Eksempel: Hvis du spiste torsk, sei  sei med mer etter dette, har du tolal  kryss i boksen for 2 ganger per mån  Middag med fjørfe  Grillet kylling  Enkelte steder kan du skrive tekst  — Skriv tydelig  — Skriv bare tekst når du blir i  Så snart du har fyli.	ike på h mm til n It spist ti ned slik;	5+	har sp 1 1 gan 1 1 gan 2 g sei 2 4 1	ist bety ist det g i uke 4 gang pr. uke 3	siste å å an i 6 n n i	i om a svark	angi et g r på rad, snitt blir eer 3 3 + at du s convolu	jennon det for dette 2	nsnitt. rste halv ganger måned 1	ve året, r r per må	men ik	kke hari	

Oppgi dag, måned og år for utfylling av skjemaet

dag måned år

(skriv årstall med 4 tall, f.eks. 2006)

100	Kostvaner			E175		2777	1 Town 10	8,1 n	Mari	2819	21/25	1874	Electric Control	9 11 20 11	
	Costvaner													ile.	
1	. Hvordan vil du beskrive dine kostvaner de	at elete	året?												
		or olote	uiot.					+	-				bare		
	ostvaner											ett k	ryss		
	. I mitt kosthold inngår kjøtt og fisk														
	. Jeg unngår kjøtt, men spiser fisk														
	. Jeg unngår fisk, men spiser kjøtt											L			
	. Jeg er vegetarianer og inkluderer melkeprod						_								
	. Jeg er vegetarianer og inkluderer melkeprod							etarian	ier)			_			
ь	. Jeg er vegetarianer og utelater alle melkepro	aukter	og egg	j tra ke	osten (	vegan	er)					L			
															+
	. Har du brukt økologiske matvarer det sist	e aret				,				0.6					
	ikologisk matvare		Sjeld	ont/ald	arı	Noci	n gang	or		Ofte		For det	t meste	9	
	. Melk, melkeprodukter og ost									Ц		L			
	. Brød og kornprodukter (f. eks. mel, müsli)											_			
	. Egg							4:							
	. Grønnsaker														
	Frukt +									H		_			
6.	. Kjøtt +											L			
	Antall måltider	919	1		100	19.5	2/5/5		560	AL ST	10 43		145		W11-12
-	Antan maitidei		14000		ورياب		123		4	90	99.5	650			
	. Hvor ofte har du i gjennomsnitt spist følge								us alla		at Mall	4 (4)			
b	t mellommåltid er et mindre måltid som for eks estår av drikke skal <u>ikke</u> tas med da det blir sp	semper	kan be er drikk	esta a	rrukt, ere. <i>(S</i>	ett bai	polle, re ett k	yognu ryss p	irt elle å <i>hvel</i>	r goate <i>linje.)</i>	eri. Meli	ommaiti	ider so	m bare	
								der pr.							
		7		6	5	Anta	4	aer pr.	uke	2	1	(	0		
1.	Frokost														
2.	. Mellommåltid, formiddag														
3.	Formiddagsmat														
4.	. Mellommåltid, ettermiddag														
5.	Middag														
6.	. Mellommåltid, kveld														
7.	Kveldsmat														+
8.	Nattmat														
	Pred knokkobred kie	100	SELE.	1000	1 162	25	100	7745Y	77 100			A Color	T - 1	4 6	
	Brød, knekkebrød, kje	KS			54									8.7	
	· 5.														
	Hvor mange skiver brød/knekkebrød/kjeks														+
	år du svarer på spørsmålene, skal du tenke pa baguett = 4 skiver brød, 1 ciabatta = 3 skiver								vt run	dstykke	e = 1 sl	rive brø	d,		
	zagada - o dator zizaj i dazama - o dator	51241 (	JOH DU	70 011											
		ſ				Antall pr. 0		kiver/ki	nekkel	orød/kj	<u>eks</u>		eller p	r uko	
В	rødtype	13+	9-12	8	7	6	5	4	3	2	1	5-6	3-4	1-2	0
1.	Fint brød (loff, baguetter, ciabatta o.l.)														
2.	Mellomgrovt brød (kneipp, husholdn.brød)														
3.	Grovt brød (fiberkneipp, rugbrød o.l.)														
	Klibrød, kli-knekkebrød, rugsprø														
	Knekkebrød, skonrokk grov o.l.														
	Smørbrødkjeks (Kaptein kjeks o.l.)														
	, ,					_		_		_	_				

4 5. Bruker du smør/margarin på brød/knekkebrød/kjeks? + ☐ Nei (gå til spørsmål 8) 6. Hvis du bruker smør/margarin, på hvor mange skiver i gjennomsnitt og hvilken type smør/margarin bruker du? (Sett bare ett kryss på hver linje.) Antall brødskiver pr. dag eller pr. uke Type smør/margarin 13+ 9-12 8 3 5-6 3-4 1. Smør/Bremvk 2. Hard margarin (Per, Melange) 3. Brelett 4. Myk margarin (Soft, Vita, Olivero o.l.) 5. Lett margarin (Soft light, Vita lett, o.l.) 7. Hvor tykt lag med smør/margarin smører du på brødskivene? + Middels Skrapet + Pålegg på brød, knekkebrød, kjeks 8. Hvor mange brødskiver med de følgende påleggstypene har du spist i gjennomsnitt det siste året? + (Sett bare ett kryss på hver linje.) Antall brødskiver med dette pålegg eller pr. uke 5-6 3-4 1-2 eller pr. måned 2 1 pr. dag Ost 6+ 3 1. Brunost (Gudbrandsdalsost o.l.) 2. Brunost lettvarianter, prim 3. Hvit ost, kremost, smøreost o.l. 4. Lettvarianter av hvit ost, smøreost 5. Muggoster (Camembert, Norzola o.l.) 6. Annet ostepålegg Fiskepålegg 7. Kaviar 8. Makrell/sardin i tomat 9. Sardin i olje 10. Røkt laks/ørret/makrell 11. Sild (sursild o.l.) 12. Reker 13. Krabbe 14. Tunfisk 15. Svolværpostei (postei av fiskelever/rogn) 16. Annet fiskepålegg Kjøttpålegg 17. Magert kjøttpålegg (skinke, roast biff o.l.) 18. Servelat, lammerull, kalverull 19. Salt pølse, spekepølse, salami 20. Kalkun- og kyllingpålegg 21. Leverpostei 22. Annet kjøttpålegg forts.

				Antall I	brødskiver	r med dette					
Andre typer pålegg	6+	5	pr. dag 4 3	2	1 5	eller pr. u 5-6 3-4	1-2	3	eller pr	mane 1	0
23. Salater med majones (rekesalat	t o.l.)										
24. Frokostsalat											
25. Majones											
26. Syltetøy	+ 🗆										
27. Honning											
28. Peanøttsmør											
29. Annet nøttepålegg (Nugatti o.l.)											
30. Annet søtt pålegg (Sjokade, Hap	på o.l.)										
31. Vegetabilske posteier (Tartex o.l.	.)										
32. Frukt (banan, eple o.l.)											
33. Grønnsaker (tomat, agurk o.l.)											
<ul> <li>Hvor mange egg har du spist i (Sett bare ett kryss på hver linje.)</li> <li>Egg</li> <li>Egg, stekt, kokt, eggerøre, omelett</li> </ul>	+		pr. dag		eller p	pr. uke 3-4 1-2			pr. mår 1		
Frokostgryn, grø	<b>t</b> gryn eller grøt i g	jennon	nsnitt det	siste året'	? Derson	n du har sp	ist diss	e matva	arene til	andre	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, a. 2. Sætet måsli og måsli med frukt, no 3. Havregrøt, annen grøt 4. Cornflakes, Frosties o.l.	gryn eller grøt i g det med her. (Set All-Bran Flaxes o.l	jennom t bare e	pr. dag 2+	siste året' å hver linje	? Dersom .) ! eller; 5-6 3	n du har sp Hvor ofte pr. uke I-4 1-2	ist diss		pr. mår	0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, n  3. Havregrøt, annen grøt  4. Cornflakes, Frosties o.l.  5. Sukker på frokostgryn/grøt	gryn eller grøt i g det med her. (Set All-Bran Flaxes o.l	jennom t bare e	pr. dag 2+	siste året' å hver linje	? Dersom .) ! eller; 5-6 3	n du har sp Hvor ofte pr. uke 1-2	ist diss	eller 2-3	pr. mår 1	0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, n  3. Havregrøt, annen grøt  4. Cornflakes, Frosties o.l.  5. Sukker på frokostgryn/grøt	gryn eller grøt i g det med her. (Set All-Bran Flaxes o.l	jennom t bare e	pr. dag 2+	siste året' å hver linje	? Dersom .) ! eller; 5-6 3	n du har sp Hvor ofte pr. uke I-4 1-2	ist diss	eller 2-3	pr. mår 1	0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Gret, frokostgryn  1. Ussetede komblandinger (4-kom, n. 2. Setet müsli og müsli med frukt, nr 3. Havregret, annen gret 4. Cornflakes, Frosties o.l. 5. Sukker på frokostgryn/gret 6. Syltetey på frokostgryn/gret	gryn eller grot i g det med her. (Sel All-Bram Flaces o.l	jennom t bare e	pr. dag 2+	siste året' å hver linje	? Dersom .) ! eller; 5-6 3	n du har sp Hvor ofte pr. uke I-4 1-2	ist diss	eller 2-3	pr. mår 1	0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, n. 3. Havregrøt, annen grøt 4. Cornilakes, Frosties o.l. 5. Sukker på frokostgryn/grøt 5. Syltetey på frokostgryn/grøt  Drikke	gryn eller gret i g det med her. (Sei All-Bram Flaces o.) øtter	ijennom tt bare e	pr. dag 2+	siste året' å hver linje	? Dersom .) eller r 5-6 3	n du har sp Hvor ofte pr. uke 1-4 1-2	med m	eller 2-3	pr. mår 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost mållider enn frokost skal du også ta  13. Tent, frokostgryn  1. Usetede komblandinger (4-kom, n. 13. Havregret, annen gret 1. Cornilakes, Frosties o.l. 15. Sukker på frokostgryn/gret 15. Syltetey på frokostgryn/gret  16. Trikke  17. Hvor mange glass/kopper av f	gryn eller gret i g det med her. (Sei All-Bram Flaces o.) øtter	ijennom tt bare e	pr. dag 2+	siste året' å hver linje 1 1 1 2 3 3 3 3 4 4 4 4 5 4 5 6 6 6 7 6 7 7 8 7 8 7 8 7 8 7 8 7 8 7 8	? Dersom) eller r 5-6 3	n du har sp Hvor ofte pr. uke 1-2 1-3 1-3 1-3 1-3 1-3 1-3 1-3 1-3	med m	eller 2-3	pr. mår 1	0	
Frokostgryn, grø  10. Hvor ofte har du spist frokost mållider enn frokost skal du også ta  11. Usetede komblandinger (4-kom, 12. Setet müsli og müsli med frukt, nr 13. Havregret, annen gret 14. Cornflakes, Frosties o.l. 15. Sukker på frokostgryn/gret 15. Syltetey på frokostgryn/gret  16. Trikke  17. Hvor mange glass/kopper av frokostgryn/gret. 1 krus = 1 glass	gryn eller grot i g det med her. (Sel All-Bran Flaxes o.l otter  + folgende har du d = 2 kopper = 2,5 d	ijennom tt bare e	pr. dag 2+	siste året' å hver linje	? Dersom) eller r 5-6 3	n du har sp Hvor ofte pr. uke -4 1-2	med m	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	nâned 0
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Gret, frokostgryn  1. Ussetede komblandinger (4-kom, n.  2. Setet müsli og müsli med frukt, nr  3. Havregret, annen gret  4. Cornflakes, Frosties o.l.  5. Sukker på frokostgryn/gret  5. Syltetey på frokostgryn/gret  Drikke  11. Hvor mange glass/kopper av frokostgryn/gret. 1 krus = 1 glass s	gryn eller grot i g det med her. (Sei All-Bran Flaxes o.1 otter + følgende har du d = 2 kopper = 2,5 d	ijennom tt bare e	pr. dag 2+	siste året' å hver linje  1  nsnitt det kke = 2 gla	? Dersom .) eller r 5-6 3	n du har sp  Hvor ofte pr. uke -4 1-2	med m ss på h	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, a. 3. Havregrøt, annen grøt 4. Cornflakes, Frosties o.l. 5. Sukker på frokostgryn/grøt  5. Syltetøy på frokostgryn/grøt  Drikke  11. Hvor mange glass/kopper av frokostgryn/grøt. 1 krus = 1 glass:  Welk og yoghurt  1. H-melk, kefir, kulturmelk	gryn eller grot i g det med her. (Sel All-Bran Flaces o.) sotter  + lolgende her du d = 2 kopper = 2,5 d	ijennom tt bare e	pr. dag 2+	siste året' å hver linje 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Poerson  eller poerson  siste året  hvo  2-3 1	n du har sp  Hvor ofte pr. uke 4 1-2	med m ss på h	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, , 3. Havregrøt, annen grøt 4. Cornflakes, Frosties o.l. 5. Sukker på frokostgryn/grøt 5. Syltetey på frokostgryn/grøt  11. Hvor mange glass/kopper av frokostgryn/grøt  12. Helle kefir, kulturmelk 13. H-melik, kefir, kulturmelk 14. Lettmelk	gryn eller grot i g det med her. (Sei All-Bran Flaces o.l otter  + lolgende har du d = 2 Kopper = 2,5 d	ijennom tt bare e	pr. dag 2+  pr. dag 2+  i gjennon rs plastflas	siste året' å hver linje  1  Insnitt det kke = 2 gla  pr. dag -7 4-5	Poerson  eller poerson  siste året  hvo  2-3 1	n du har sp  Hvor ofte pr. uke 1-2 1-3 1-3 1-3 1-4 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7	med m ss på h	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, n. 3. Havregret, annen grøt 4. Cornilakes, Frosties o.l. 5. Sukker på frokostgryn/grøt 5. Syltetey på frokostgryn/grøt  Drikke  11. Hvor mange glass/kopper av frokostgryn/grøt. 1 krus = 1 glass si  Melk og yoghurt 1. H-melk, kefir, kulturmelk 2. Lettmelk 8. Ekstra lett lettmelk	t gryn eller grot i g det med her. (Sei All-Bran Flaces o.l atter  + leigende har du d = 2 Kopper = 2,5 d  (1 glass) (1 glass)	ijennom tt bare e	pr. dag 2+  pr. dag 2+  i gjennon rs plastflas	siste året* å hver linje  1  nsnitt det ike = 2 gla  pr. dag 7 4-5	Porson  Seller porson	n du har sp Hvor ofte pr. uke 1-4 1-2 1-3 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7	med n sss på h ass/bec 3-4	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usøtede komblandinger (4-kom, n. 3. Havregret, annen grøt  4. Cornilakes, Frosties o.l.  5. Sukker på frokostgryn/grøt  5. Syltetey på frokostgryn/grøt  Drikke  11. Hvor mange glass/kopper av frokostgryn/grøt  14. H-melk, kefir, kulturmelk  2. Lettmelk  8. Ekstra lett lettmelk  8. Ekstra lett lettmelk  8. Skummet melk søt, sur	gryn eller gret i g det med her. (Sei All-Bram Flaxes o.l etter  +  loigende har du d = 2 kopper = 2,5 d  (1 class) (1 class) (1 glass) (1 glass)	ijennom tt bare e	pr. dag 2+  pr. dag 2+  i gjennon rs plastflas	siste året' å hver linje  1  nsnitt det ikke = 2 gla  pr. dag 4-5	eller properties of the state o	n du har sp Hvor ofte pr. uke 1-4 1-2 1-3 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7 1-7	med m sss på h ass/beg Gller pr. 3-4	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0
Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Gret, frokostgryn  1. Usstede komblandinger (4-kom, n. 3. Havregret, annen gret 4. Cornflakes, Frosties o.l. 5. Sukker på frokostgryn/gret 5. Sukker på frokostgryn/gret  Drikke  11. Hvor mange glass/kopper av f rokostgryn/gret. 1 krus = 1 glass av  Melk og yoghurt 1. H-melk, kefir, kulturmelk 2. Lettmelk 3. Ekstra lett lettmelk 4. Skummet melk søt, sur 5. Cultura, alle typer	gryn eller gret i g det med her. (Sel All-Bram Flaces o.l etter  +  telgende har du d = 2 kopper = 2,5 d  (1 class) (1 class) (1 glass) (1 glass) (1 glass)	ijennom tt bare e	pr. dag 2+  pr. dag 2+  i gjennon rs plastflas	siste året' å hver linje  1  Insnitt det tike = 2 gla  pr. dag 7 4-5	eller properties of the state o	n du har sp  Hvor ofte pr. uke  -4 1-2	med m sss på h ass/beg 3-4	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0
Antall måsegg spist siste 12 måned  Frokostgryn, grø  10. Hvor ofte har du spist frokost måltider enn frokost skal du også ta  Grøt, frokostgryn  1. Usetede komblandinger (4-kom, a  2. Setet müsli og müsli med frukt, nr  3. Havregret, annen grøt  4. Cornflakes, Frosties o.l.  5. Sukker på frokostgryn/grøt  3. Syltetøy på frokostgryn/grøt  Drikke  11. Hvor mange glass/kopper av frokostgryn/grøt. 1 krus = 1 glass :  Melk og yoghurt  1. H-melk, kefir, kulturmelk  2. Lettmelk  3. Eksta lett lettmelk  4. Skummet melk søt, sur  5. Cultura, alle typer  5. Biola drikke, Biola yoghurt  7. Yoghurt, naturell/frukt	gryn eller grot i g det med her. (Sel All-Bram Flares o.l otter  + lotgende her du d = 2 kopper = 2,5 d  (1 glass) (1 glass) (1 glass) (1 glass) (1 glass)	ijennom tt bare e	pr. dag 2+  pr. dag 2+  i gjennon rs plastflas	siste året' å hver linje  1  Insnitt det tike = 2 gla  pr. dag 7 4-5	eller r 5-6 3	n du har sp  Hvor ofte pr. uke  -4 1-2	med m sss på h ass/beg 3-4	eller 2-3	pr. mår 1	o o o o o o o o o o o o o o o o o o o	0

(1 beger) (1 glass) (1 glass) (1 glass)	8+	6-7	pr. dag 4-5	2-3	1	5-6	3-4	1-2	2-3	pr. mår 1	0
(1 glass) (1 glass)											
(1 glass)											
(1 glass)											
					Hyor	mange	alaee				
	8+	6-7	pr. dag 4-5	2-3	1		dia33 ler pr. 1 3-4	1-2	eller 2-3	pr. mår 1	ned 0
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
(1 glass)											
				П		1000000					
(1 glass)											
				П	П						
(1 dram)											
(1 dram)	8+	6-7	pr. dag		Hvor me	nge kor	pper/kr er pr. u			pr. mår	ned 0
		6-7	pr. dag		Hvor me	nge kor	er pr. u	us like	eller		
(1 kopp) (1 kopp)		6-7	pr. dag		Hvor me	nge kor	er pr. u	us like	eller	1	
(1 kopp) (1 kopp)		6-7	pr. dag		Hvor me	nge kor	er pr. u	us like	eller	1	
(1 kopp) (1 kopp) (1 kopp)		6-7	pr. dag		Hvor me	nge kor	er pr. u	us like	eller	1	0
(1 kopp) (1 kopp) (1 kopp) (1 kopp)	8+	6-7	pr. dag 4-5	2-3	Hvor me	ngc kop ell 5-6	3-4	us like	eller 2-3	1	0
(1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp)	8+	6-7	pr. dag 4-5	2-3	Hvor me	ngc kop ell 5-6	3-4	us like	eller 2-3	1	0
(1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp)	8+	6-7	4-5	2-3	dvor me	nge kor ell 5-6	3-4	us like 1-2	eller 2-3		0
(1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp)	8+	6-7	4-5	2-3	dvor me	nge kop ell 5-6	9-4 S-4 S-4 S-4 S-4 S-4 S-4 S-4 S-4 S-4 S	us like 1-2	eller 2-3	1	0
(1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp) (1 kopp)	8+	6-7	4-5	2-3	1	nge kop ell 5-6	3-4	us like 1-2	eller 2-3		0
	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)	(1 glass)

24. Lever, nyre fra sau25. Lever, nyre fra vilt26. Blodmat, lungemos

+

7 Middagsmat (varm mat) Først ber vi deg svare på et generelt spørsmål om ulike grupper av varm mat. Deretter ber vi deg svare mer i detalj på de ulike typene av varm mat du har spist det siste årst. Når du svarer på disse spørsmålene, ber vi deg å tenke på både middagsmat og annen varm mat du eventuelt spiser i løpet εν dagen. 13. Hvor ofte har du i gjennomsnitt spist følgende type varm mat det siste året? (Sett bare ett kryss på hver linje.) eller pr. måned Generelle spørsmål 6+ 5 2 3 1. Kjøtt og kjøttprodukter 2. Kjøtt og kjøttprodukter, grillet 3. Innmat 4. Kylling, kalkun 5. Fisk, fiskeretter, kokt, ovnsbakt 6 Fisk fiskeretter stekt 7. Vegetarretter Mer detaljerte spørsmål om hver enkelt middagsrett + 14. Hvor ofte har du i gjennomsnitt spist følgende typer varm mat det siste året? (Sett bare ett kryss på hver linje.) Hvor ofte eller pr. måned Middag med blandingsprodukter av kjøtt 6+ 5 1. Kjøttpølser, medisterpølser 2. Grillpølser, wienerpølser 3. Kyllingpølser, kalkunpølser 4. Kjøttkaker, medisterkaker, kjøttpudding 5. Hamburgere, karbonader 6. Kiøttdeig i saus el. gryteretter Middag med okse-/ kalvekjøtt 7. Oksestek, kalvestek 8. Biff (indrefilet, løvbiff, mørbrad, entrecote) 9. T-bone stek, kalvekotelett 10. Kjøttgryte, lapskaus, kjøttsuppe Middag med svinekjøtt 11. Kotelett, nakkekotelett, skinkestek 12. Indrefilet, flatbiff 13. Sommerkotelett, hamburgerrygg 14. Flesk, ribbe, "spare ribs" 15. Bacon 16. Gryterett Middag med lam/sau 17. Lammestek, lammekotelett 18. Gryteretter med lam/sau (Får i kål o.l.) Middag med viltkjøtt 19. Reinsdyrstek 20. Stek av elg, hjort, rådyr 21. Reinsdyrkaker, gryterett av reinsdyr 22. Karbonader, gryterett (elg, hjort, rådyr) Middag med innmat 23. Lever, nyre fra okse, gris

forts.

Hvor ofte + pr. uke eller pr. måned Middag med fjørfe 0 27. Kyllingfilet, kalkunfilet 28. Grillet kylling 29. Stekt/kokt kylling, høne og kalkun 30. Kyllingschnitzel, nuggets 31. Viltfugl (rype, orrfugl o.l.) 32. Annet fjørfe (and, gås, struts) Middag med fisk/sjømat 33. Torsk, sei, kolje, lyr (kokt/stekt/røkt) 34. Makrell, sild (kokt/stekt/røkt) 35. Laks, ørret 36. Flyndrefisker (kveite, rødspette o.l.) 37. Tunfisk (f.eks. i salat) 38. Abbor, gjedde, gjeddekaker 39 Annen ren fisk 40. Fiskekaker, fiskepudding, fiskeboller 41. Fiskepinner, fiskepanetter, panert fisk 42. Fiskegryte, fiskegrateng, suppe med fisk 43. Reker 44. Skjell 45. Krabbe + 46. Rogn 47. Fiskelever Pastaretter 48. Pastarett med kjøtt (spaghetti med kjøttsaus, Lasagne o.l.) 49. Pastarett med fisk/reker/skjell 50. Pastarett med grønnsaker 51. Pastarett med bare tomatsaus/ketchup 52. Ost (Parmesan o.l.) på pastarett Annen varm mat 53. Pizza 54. Taco, burritos o.l. 55. Pannekaker 56 Grøt (ikke frokostgrøt) 57. Suppe, hjemmelaget og posesuppe Grønnsaksrett som hovedrett 58. Bare med grønnsaker 59 Med bønner/linser 60. Med soyaprodukter (pølser, o.l.) Tilbehør til varm mat 15. Hvor ofte har du i gjennomsnitt spist følgende matvarer det siste året? (Sett bare ett kryss på hver linje.) + Hvor ofte eller pr. uke 3-4 pr. dag eller pr. måned 2-3 Poteter/ris/spaghetti 1. Poteter (kokte, bakte, potetstappe) 2. Pommes frites, stekte poteter 3. Potetstuing, gratinerte poteter 4. Spaghetti, makaroni, nudler 6. Hirse, couscous o.l. forts.

		9		
		Hvor ofte		
Saus/tilbehør	pr. dag	eller pr. uke 5-6 3-4 1-2	eller pr. måned 2-3 1 0	+
7. Smeltet smør		5-6 3-4 1-2	2-3 1 0	
8. Smeltet margarin				
9. Brun/hvit saus				
10. Bearnaisesaus o.l.				
1. Majones, remulade				
2. Seterrømme, Crème Fraîche  13. Lettrømme				
4. Ketchup				-
5. Sennep				
Type fett til matlagin	ng			
i6. Hvor ofte har du i gjennomsnitt bruk		tt i matlagingen det siste	året? (Sett bare ett kryss på hve	er linje.)
		Hvor	<u>fte</u>	+
Suna fatt til matlagin -	pr. dag	eller pr. uke	eller pr. måned	
Type fett til matlaging  1. Smør	2+ 1	5-6 3-4		0
				]
2. Bremyk, Smørgod				
Melange, Per     Seft covernormer (nakke hoger)				
Soft soyamargarin (pakke, beger)     Olivero				_
6. Annen margarin				
7. Soyaolje				
Matolje     Olivenolje				
Maisolje				
1. Andre oljer				
1. Allule oljei				
Grønnsaker				
ørst ber vi deg svare på et generelt spø 7. Hvor ofte har du i gjennomsnitt spist		ste året? (Sett bare ett kry	ss på hver linje.)	ı har spist.
	pr. dag	Hvor o eller pr. uke	fte   eller pr. måned	
versiktsspørsmål	2+ 1	5-6 3-4	1-2 2-3 1 (	)
. Rå grønnsaker i (salat, råkost o.l.)				
. Grønnsaker i gryteretter, supper, wok o.l.				
. Kokte grønnsaker som tilbehør				
Mer detaljert om hve	er enkelt g	grønnsak		
8. Hvor ofte har du i gjennomsnitt spist			are ett kryss på hver linje.)	
+	pr dos	Hvor o		
Grønnsaker	pr. dag 2+ 1	eller pr. uke 5-6 3-4	eller pr. måned 1-2 2-3 1 (	)
. Grønnsaksblandinger, frosne				
. Agurk				
. Aubergine				
5. Aubergine				

				Hvo	r ofte				
+		dag		ller pr. u			er pr. må		
Grønnsaker	2+	1	5-6	3-4	1-2	2-3	1	0	
5. Blomkål, rå									
6. Blomkål, kokt/i gryteretter									
7. Brokkoli, rå									
8. Brokkoli, kokt/i gryteretter									
9. Bønner (grønne-, aspargesbønner)				Ш					
0. Erter									
1. Gulrot, rå									
2. Gulrot, kokt/i gryteretter									
3. Hodekål, rå									
4. Hodekål, kokt/stuing/i gryteretter									
5. Hvitløk									
6. Kålrot, rå									
7. Kålrot, kokt/stappe/i gryteretter									
8. Løk, purre, vårløk, rå					4:				
9. Løk, purre, vårløk, stekt/i gryteretter									
to. Mais									
1. Paprika, rå									
2. Paprika i gryteretter									
3. Rosenkål, kokt/i gryteretter									
4. Salatblandinger, ferdig i pose									
5. Salat (bladsalat, issalat, kinakål o.l)									
6. Selleri, stilkselleri									
7. Sjampinjong, rå			П	П	П	П		П	
8. Sjampinjong, stekt/i gryteretter				П					
9. Skogsopp, annen sopp				П	П			П	
0. Spinat			П	П					
1. Squash (Zucchini)				П					
2. Tomat		П		П	П				
3. Andre grønnsaker				П					7
9. Hvor ofte har du i gjennomsnitt brukt di				Hvor	ofte				nje.)
Pressing/annet tilbehør	pr. 2+	dag 1	5-6	ler pr. ul 3-4	re 1-2	2-3	er pr. må 1	ined 0	
		'n	5-0	0-4		2-3			
Dressing (Thousand island of )									
. Lett dressing, yoghurt dressing									
. Lett dressing, yoghurt dressing . Oliven, sorte/ grønne									
. Lett dressing, yoghurt dressing . Oliven, sorte/ grønne . Fetaost									
Lett dressing, yoghurt dressing Oliven, sorte/ grønne Fetaost Jemmelaget dressing									
Lett dressing, yoghurt dressing  Oliven, sorte/ grønne  Fetaost  Jjemmelaget dressing  Med olje									
Lett dressing, yoghurt dressing  Oliven, sorte/ grønne  Fetaost  Jjemmelaget dressing  Med olje  Uten olje									
Lett dressing, yoghurt dressing Oliven, sorte/ grønne Fetaost Jjemmelaget dressing Med olje Uten olje Med rømme/yoghurt									
. Lett dressing, yoghurt dressing . Oliven, sorte/ grønne . Fetaost Iglemmelaget dressing . Med olije . Uten olije . Med rømme/yoghurt	t/grønnsake	er i gryteret	tene. (Sett b		Cryss på hv	er linje.)	+		
. Lett dressing, yoghurt dressing . Oliven, sorte/ grønne . Fetaost Iglemmelaget dressing . Med olije . Uten olije . Med rømme/yoghurt	t/grønnsake	er i gryteret	tene. (Sett b	jrønnsak	aryss på hv.	er linje.)		Mer kjøtt e	nn er
2. Lett dressing, yoghurt dressing 3. Oliven, sorte/ grønne 4. Fetaost 4. Fetaost 4. Fetaost 6. Med olije 6. Uten olije 7. Med rømme/yoghurt 7. Med rømme/yoghurt 7. Hva er omtrentlig vektforhold av kjøt	t/grønnsake	er i gryteret	tene. (Sett b		aryss på hv.	er linje.)			nn er
. Cryteretter med helt kjøtt/fisk . Gryteretter med helt kjøtt/fisk . Gryteretter med helt kjøtt/fisk . Gryteretter med island o.l.)	t/grønnsake	er i gryteret	tene. (Sett b	jrønnsak	aryss på hv.	er linje.)		Mer kjøtt e	nn er

				11									
Frukt													
21. Hvor mange friske fru	kter har du spist i	gjennom	nsnitt de	et siste	året?								
				pr. dag			ī	eller pr	uke	1	eller i	or. måi	ned
	+	8+	6-7	4-5	2-3	1	5-6					1	0
Frisk frukt	+					П						П	
							,					_	
													.1
22. Hvor ofte har du i gjer	nomsnitt spist fø	lgende fr	iske fru	kter det	siste å	ret? (Se	ett bare	ett krvs	s nå hve	r linie.)			+
							lvor ofte		,	, ,			
				dag		1	el	ler pr. ul				or. måi	
Frisk frukt		4+	3	2	1		5-6	3-4	1-2	2-	3	1	0
1. Appelsin, mandarin	(1 stykk)												
2. Banan	(1 stykk)												
3. Druer	(8-10 stykk)												
4. Eple	(1 stykk)												
5. Fersken, nektarin	(1 stykk)					- 1	¥ .						
6. Grapefrukt	(1/2 stykk)												
7. Jordbær	(¼ kurv)												
8. Andre bær (blåbær o.l)	(¼ kurv)												
9. Mango	(1/₂ stykk)												
10. Melon	(1 skive)												
11. Papaya	(1/2 stykk)												
12. Plomme	(1 stykk)												
	(1 stykk)										]		
13. Pære	(1 Styrkk)												
14. Annen frukt										[			
14. Annen frukt							t bare e	t kryss	1	, _			+
14. Annen frukt 23. Hvor ofte har du i gjer				ter det s			t bare e	t kryss	) på hver	linje.)	eller p	or. mår	+
14. Annen frukt 23. Hvor ofte har du i gjer Førket frukt /nøtter	ınomsnitt spist tøl	rket frukt	og nøti	ter det s	siste åre		t bare e	tt kryss i	oå hver	linje.)	eller p	or. mår	+
14. Annen frukt 23. Hvor ofte har du i gjer Førket frukt /nøtter 1. Aprikoser	ınomsnitt spist tøl	rket frukt	og nøti	ter det s	siste åre		t bare e	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer Førket frukt /nøtter  1. Aprikoser  2. Rosiner	ınomsnitt spist tøl	rket frukt	og nøtt	dag 2	iste åre		t bare el	ler pr. ul	på hver	linje.)	eller p	or. mår 1	+
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler	ınomsnitt spist tøl	rket frukt	og nøti	dag 2	1		t bare e	ler pr. ul	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter	nomsnitt spist to	rtet frukt	og nøti	dag 2	1		t bare el	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter	nomsnitt spist to	rtet frukt	og nøti	dag 2	1		t bare el	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
13. Pære 14. Annen frukt 23. Hvor ofte har du i gjer Tørket frukt /nøtter 1. Aprikoser 2. Rosiner 3. Svisker, fiken, dadler 4. Peanøtter 5. Mandler, hasselnøtter, ca	nomsnitt spist to	rtet frukt	og nøti	dag 2	1		t bare el	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Paanøtter	nomsnitt spist to	rtet frukt	og nøti	dag 2	1		t bare el	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca	+ tshewnetter o.l.	rtet frukt	og nøti	dag 2	1		t bare el	tt kryss i	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca	+ shewnetter o.l.	tket frukt	og nøti	dag 2	1	H	t bare en	tt kryss     der pr. ul   3-4   -	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca	+ shewnetter o.l.	tket frukt	og nøti	dag 2	1	t bare etc	t bare exists to bare exists the bare exists t	tt kryss     der pr. ul   3-4   -	på hver	linje.)	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca	+ shewnetter o.l.	tket frukt	og nati	dag 2	1	bare etc	t bare exists to bare exists the bare exists t	ler pr. ul 3-4	på hver	2	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanotter  5. Mandler, hasselnøtter, ca  Dessert, is, k	+ shewnetter o.l.	tket frukt	og nøtti	dag 2	1	bare etc	t bare exists to bare exists the bare exists t	ler pr. ul 3-4	på hver	2	eller r	or. mår 1	+ ned 0
14. Annen frukt 23. Hvor ofte har du i gjer Førket frukt /nøtter 1. Aprikoser 2. Rosiner 3. Svisker, fiken, dadler 1. Peanøtter 5. Mandler, hasselnøtter, ca Dessert, is, k 24. Hvor ofte har du i gjer	+ shewnetter o.l.  aker, goo	tret frukt	og nøtti	dag 2	1	t bare ett	t bare e	tt kryss, 3-4	på hver	2-:	eller r	or. mår 1	+ ned 0
14. Annen frukt 23. Hvor ofte har du i gjer Førket frukt /nøtter 1. Aprikoser 2. Rosiner 3. Svisker, fiken, dadler 4. Peanøtter 5. Mandler, hasselnøtter, ca Dessert, is, k 24. Hvor ofte har du i gjer Dessert/ls 1. Puddinger (sjokolade, ka	+ shewnetter o.l.  aker, goo	tret frukt	pr. 3	dag 2	1	t bare ett	t bare e	tt kryss, 3-4	på hver	2-:	eller p	or. mår 1	+ ned 0
14. Annen frukt  23. Hvor ofte har du i gjer  Førket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ce  Dessert, is, k  24. Hvor ofte har du i gjer  Dessert/ls  1. Puddinger (sjokolade, ka  2. Hermetisk frukt, fruktgrøt	+ shewnetter o.l.  aker, goo	4+	pr. 3	2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1	t bare ett	t bare e.e.  5-6	ler pr. ul 3-4	på hver	2	eller p	or. mår 1	+  hed 0
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ce  Dessert, is, k  24. Hvor ofte har du i gjer  Dessert/ls  1. Puddinger (sjokolade, ka  2. Hermetisk frukt, fruktgrøt  3. Fruktsalat med frisk frukt	+ shewnetter o.l.  aker, goo	4+	pr. 3	2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1	t bare ett	t bare e.e.  5-6	itt kryss, ler pr. ui 3-4	på hver	2	eller p	or. mår 1	+ + hed o o o o o o o o o o o o o o o o o o o
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14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Paanøtter	the shewnetter o.l.  taker, good anomanitt spist de framell o.l.)	4+	og natt	ter det s 2 2 iste åre	1	t bare ett	t kryss p	tt kryss i se pr. ul 3-4	på hver	2-:-	eller p	or. mår 1	+ + control co
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanetter  5. Mandler, hasselnøtter, ca  Dessert, is, k  24. Hvor ofte har du i gjer  Dessert/Is  1. Puddinger (sjokolade, ka  2. Hermetisk frukt, fruktgrøt  3. Fruktsalat med frisk frukt  4. Floteis  5. Yoghurtis, lettis	+ shewnetter o.l.  aker, goo	4+	og natt	ter det s 2 2 iste åre	1	bare etc	t kryss p	tt kryss , see see see see see see see see see	på hver	2-:-	eller r r g	or. mår 1	+ + contract
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca  Dessert/, is, k  24. Hvor ofte har du i gjer  Dessert/ls  1. Puddinger (sjokolade, ka  2. Hermetisk frukt, fruktgret  3. Fruktsalat med frisk frukt  4. Floteis  5. Yoghurlis, lettis  6. Saftis, sorbet  7. Vaniljesaus	the shewnetter o.l.  taker, good anomanitt spist de framell o.l.)	4+	og netti	ter det s 2 2 iste åre	1	bare etc	t kryss p	tt kryss , 3-4	på hver	2	eller r r g	or. mår 1	+ + hand o o o o o o o o o o o o o o o o o o o
14. Annen frukt  23. Hvor ofte har du i gjer  Tørket frukt /nøtter  1. Aprikoser  2. Rosiner  3. Svisker, fiken, dadler  4. Peanøtter  5. Mandler, hasselnøtter, ca  Dessert, is, k  24. Hvor ofte har du i gjer  Dessert/ls  1. Puddinger (sjokolade, ka  2. Hermetisk frukt, fruktgrøt  3. Fruktsalat med frisk frukt  4. Floteis  5. Yoghurtis, lettis  6. Saftis, sorbet	the shewnetter o.l.  taker, good anomanitt spist de framell o.l.)	4+	og netti	ter det s 2 2 iste åre	1	bare etc	t kryss p	tt kryss ,	på hver	2	eller r r g	or. mår 1	+ + hand o o o o o o o o o o o o o o o o o o o

				A office of			vec nå hv	or linio )				
25. Hvor ofte har du i gjennor	nsnitt spist ka	aker og b	oller de	et siste a	aretr (Sett	bare ett kr						
						Hvor o						
Kaker, boller		4+	pr.	dag	1	5-6	eller pr. u 3-4	1-2		ellei 2-3	r pr. ma	aned 0
Boller, julekake o.l.	(1 stykke)				Ė						Ċ	
2. Wienerbrød, wienerstang o.l.												
3. Smultring, fyrste- formkake	(1 stykke)											
4. Vafler	(1 plate)											
5. Sjokoladekake, bløtkake o.l.	(1 stykke)											
6. Søt kjeks, kakekjeks	(1 stykke)											
26. Hvor ofte har du i gjennor	msnitt spist go	odteri de	t siste å	ret? (So	ett hare ett	kryss nå h	ver linie )					+
3				100	ou our o ou	Hvor o						
Carltoni on angels	+	4+	pr.	dag 2	1	5-6	eller pr. u	1-2	1	ellei	r pr. má	aned
Godteri og snacks  1. Ren sjokolade					Ė	5-6	3-4	1-2		2-3	1	0
Sjokolade med nøtter o.l.						[4:]				$\overline{\Box}$		
Karameller, konfekt, lakris										П	П	
4. Smågodt, seigmenn		П								П		
5. Pastiller med sukker										ī		
Pastiller uten sukker		П								П		
7. Marsipan	+	П	П	П	П					ī		
8. Potetgull, potetskruer		П		П								
Of Fotorgam, perceton and											П	
9 Poncorn												
9. Popcom 10. Saltstenger, lettsnacks o.l.  Andre matvare		matvare	or som (	du kan l	na spist de	t siste åre	t ber vi d	eg nede	enfor å	skrive	navn	et på
10. Sallstenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi	spurt om alle	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Saltstenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få	spurt om alle t og som det i	e matvare	er som ditt spur	t etter.			fte			elle		
10. Sallstenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi	spurt om alle t og som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Sallstenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spist	spurt om alle t og som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Sallstenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spist  Andre matvarer	spurt om alle t og som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Salistenger, lettsnacks o.l.  Andre matvare 27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer Navn: Navn:	spurt om alle t og som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Salistenger, lettsnacks o.l.  Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spist  Andre matvarer  Navn:	spurt om alle t og som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spist  Andre matvarer  Navn: Navn:	spurt om allet tog som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
10. Salistenger, lettsnacks o.l.  Andre matvare 27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer Navn: Navn:	spurt om allet tog som det i	e matvare	litt spur	pr. da	ag	Hvor o	fte el	ler pr. ul	ke	elle	er pr. n	nåned
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi  Andre matvarer  Navn:  Navn:  Navn:  Genmodifisert  28. I mange land, bi.a. USA, E merking ved salg av genmodi	spurt om alle t og som det i +  mat  mgland, og Friffserte matvar	e matvardikke er bi	5	pr. da 4	3 2	Hvor o	fite el 5-6	Jeffes	ke 1-2	elle	er pr. n 2-3	håned 1
10. Sallstenger, lettsnacks o.l.  Andre matvare 27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer Navn: Navn: Navn: Genmodifisert 28. I mange land, bl.a. USA, E	spurt om allet tog som det i  +  mat  ngland, og Fratiserte matvareliser eller i No	e matvardikke er bi	5	pr. da	ag 3 2	Hvor o	natvarer.	ler pr. ui 3-4	ke 1-2	elle	er pr. n 2-3	håned 1
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi  Andre matvarer  Navn:  Navn:  Navn:  Genmodifisert  28. I mange land, bi.a. USA, E merking ved salg av genmodi	spurt om alle t og som det i +  mat  mgland, og Friffserte matvar	e matvardikke er bi	5	pr. da 4	ag 3 2	Hvor o	fite el 5-6	ler pr. ui 3-4	ke 1-2	elle	er pr. n 2-3	håned 1
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Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer  Navn: Navn: Navn: Genmodifisert  28. I mange land, bl.a. USA, E merking ved salg av genmodi modifiserte ingredienser på re  29. Hvis ja, ber vi deg skrive r	spurt om allet tog som det i  +  mat  ingland, og Friffiserte matvareiser eller i No	e matvarrkkeer bl	5	pr. de deter.  pr. de	ag 3 2	Hvor o	natvarer.  Vet iki	De fles matvare	1-2	elle	e land rer me	håned  1  krever d gen-
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer  Navn: Navn: Navn: Cenmodifisert  28. I mange land, bl.a. USA, E merking ved salg av genmodi modifiserte ingredlenser på re  29. Hvis ja, ber vi deg skrive r  Genmodifiserte matvarer	spurt om allet tog som det i  +  mat  ingland, og Friffiserte matvareiser eller i No	e matvaren e matvaren e matvaren e matvaren e matvaren e e e e e e e e e e e e e e e e e e	5  itillater n sker å	pr. de 4 4 4 In an an salque om et.	ag 3 2	Hvor o	natvarer.  Vet ikk	De fles matvare	1-2	elle	er pr. n 2-3	håned 1
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer  Navn: Navn: Navn: Genmodifisert  28. I mange land, bl.a. USA, E merking ved salg av genmodi modifiserte ingredienser på re  29. Hvis ja, ber vi deg skrive r	spurt om allet tog som det i  +  mat  ingland, og Friffiserte matvareiser eller i No	e matvaren e matvaren e matvaren e matvaren e matvaren e e e e e e e e e e e e e e e e e e	5	pr. de deter.  pr. de	ag 3 2	Hvor o	natvarer.  Vet iki	De fles matvare	1-2	elle	e land rer me	håned  1  krever d gen-
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer  Navn: Navn: Navn: Cenmodifisert  28. I mange land, bl.a. USA, E merking ved salg av genmodi modifiserte ingredlenser på re  29. Hvis ja, ber vi deg skrive r  Genmodifiserte matvarer	spurt om allet tog som det i  +  mat  ingland, og Friffiserte matvareiser eller i No	e matvaren e matvaren e matvaren e matvaren e matvaren e e e e e e e e e e e e e e e e e e	5	pr. de deter.  pr. de	ag 3 2	Hvor o	natvarer.  Vet iki	De fles matvare	1-2	elle	e land rer me	håned  1  krever d gen-
Andre matvare  27. Fordi det er vanskelig å få matvarer som du kan ha spisi Andre matvarer  Navn: Navn: Navn: Cenmodifisert  28. I mange land, bl.a. USA, E merking ved salg av genmodi modifiserte ingredienser på re  29. Hvis ja, ber vi deg skrive r  Genmodifiserte matvarer	spurt om allet tog som det i  +  mat  ingland, og Friffiserte matvareiser eller i No	e matvaren e matvaren e matvaren e matvaren e matvaren e e e e e e e e e e e e e e e e e e	5	pr. de deter.  pr. de	ag 3 2	Hvor o	natvarer.  Vet iki	De fles matvare	1-2	elle	e land rer me	håned  1  krever d gen-

Varm mat fra kiosk, be	ensinstasjo	on elle	r gatekje	kken		No.
30. Hvor ofte har du i gjennomsnitt spist va	ım mat fra kiosk, ber	nsinstasjon e	ller gatekjøkken	det siste året?		
,			Hvor o	fte		
Mat fra	pr. dag 4+ 2-3	1	eller pr. u 5-6 3-4	ke 1-2	eller pr. må 2-3 1	ned
1. Kiosk	4+ 2-3		5-6 3-4	1-2	2-3 1	0
2. Bensinstasjon						
Gatekjøkken, McDonald's o.l.		П		П		
o. datelyphich, Moboliaid's cit.	0 0					
Kostendringer i livet o	i++				Car 7 (2)	
				water a second dead	o la ella	
31. Nedenfor ber vi deg angi om du spiser/c eventuelt da du var barn (før fylt 18 år).	rikker mer, minare e	lier samme n	nengde sammen	liknet med for a	30 ar siden,	
Matvare	Spiste/drakk det heller ikke før	Som før	Mer	Mindre	Sluttet	
1. Krabbe			NIGI	TVIII I I I I	Tiell	
2. Reker			*			+
Skjell (for eksempel blåskjell)				П		
Skjell (for eksempel blaskjell)     Fiskelever (ikke tran)						
5. Tunfisk eller Kveite 6. Flyndre/annen flatfisk +			_			
9210-12 10 10 10 10 10 10 10 10 10 10 10 10 10						
7. Gjedde (kaker) eller abbor					_	
8. Annen ferskvanns fisk						1
9. Reinsdyr						
10. Sau / lammekjøtt						
11. Lever eller nyre fra vilt						
12. Viltvoksende sopp						
13. Måsegg						
+						+
	+					

ts = teskje, bs = barneskje, ss = spiseskje)	de neden	for.											
Flytende kosttilskudd	7	6	A 5	ntall g	ange 3	pr. u	ke 1	<1	0		de pr. 1bs		
I. Tran			П	П			П	П			П		
2. Omega-3 tran +													
3. Sanasol													
1. Biovit													
5. Flytende jernmixtur (Floradix o.l.)													
Annet flytende kosttilskudd													
S. Navn:							k:					П	
7. Produsent:									ш		Ш	Ш	
3. Navn:	П			П			П						
9. Produsent:													
<b>Capsler/tabletter</b> 10. Trankapsler	7	6	5 	ntall g	anger	pr. u 2	ke 1	<1	0	1 □	ntall p	or. gan	g 4+
1. Fiskeoljekapsler													
2. Vitaplex, B-vitaminer													
3. Kostpluss Collett/Nycovit kostpluss													
4. Nyco plus folsyre 0,4 mg													
5. Spektro (Solaray)			Н										
7. Duroferon duretter, Ferro Retard		П	П		П		П	П					
Andre kosttilskudd 8. Navn:				4									
o. Navii.		П	П										
			_				_		_		_		
9. Produsent:													
9. Produsent: 20. Navn:													
20. Navn: 21. Produsent:													
20. Navn:													
20. Navn: 21. Produsent:									_				
20. Navn: 21. Produsent: 22. Navn:									_				