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Doctoral thesis

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Irritable bowel syndrome in subjects with morbid obesity

Observational studies of patients at outpatient clinics

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Thesis for the Degree of
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Irritabel tarm-syndrom ved sykelig overvekt
Observasjonsstudier av pasienter rekruttert fra poliklinikker

Forekomsten av irritabel tarm-syndrom (IBS) ble undersøkt blant pasienter med sykelig overvekt henvist til vurdering ved to fedmepoliklinikker. Fordi både IBS og sykelig overvekt har vært assosiert med lavgradig betennelse og unormal tarmflora (dysbiose), var det ventet å finne en høy forekomst. Forekomsten ved Sykehuset Innlandet – Gjøvik og Oslo Universitetssykehus – Aker var henholdsvis 27% (37/139) og 8% (17/211). Den store forskjellen mellom de to poliklinikkene kunne ikke sikkert forklares, men samlet ser det ut til at IBS er vanligere blant pasienter med sykelig overvekt enn i den generelle befolkningen. Fordi IBS var assosiert med høyere verdier av LDL-kolesterol i blodet og mer selvrapporterte psykiske plager synes kostholdet og psykiske faktorer å bidra til den høye forekomsten.Symptomene ble betydelig redusert i løpet av en 6 måneders periode med kost- og livsstilsendringer og 10 kg vekttap. En ny test for dysbiose viste høy forekomst av dysbiose men kunne ikke skille mellom pasienter med og uten IBS. Samlet ga ikke resultatene holdepunkter for at den høye forekomsten av IBS skyldes verken lavgradig betennelse eller dysbiose. Avhandlingen er basert på tre publiserte artikler, to tverrsnittsstudier og en prospektiv kohortestudie. Alle studiene bygger på datamateriale fra Sykehuset Innlandet Gjøvik innsamlet fra 2012 til 2014. Studiene benytter også datamateriale fra Oslo Universitetssykehus, Aker og Lovisenberg Diakonale Sykehus.

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Disputas finner sted på NTNU Gjøvik
Fredag 19. oktober 2018

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Paper I **Aasbrenn M,** Høgestøl I, Eribe I, Kristinsson J, Lydersen S, Mala T, Farup PG. Prevalence and predictors of irritable bowel syndrome in patients with morbid obesity: a cross-sectional study. BMC Obesity. 2017;4:22.
doi: 10.1186/s40608-017-0159-z

Paper II **Aasbrenn M,** Valeur J, Farup PG. Evaluation of a faecal dysbiosis test for irritable bowel syndrome in subjects with and without obesity. Scandinavian Journal of Clinical and Laboratory Investigation 2018;78(1-2):109-113.
doi: 10.1080/00365513.2017.1419372

Paper III **Aasbrenn M,** Lydersen S, Farup PG. A conservative weight loss intervention relieves bowel symptoms in morbidly obese subjects with irritable bowel syndrome – a prospective cohort study. Journal of Obesity 2018. Article ID 3732753.
doi: 10.1155/2018/3732753

Abbreviations

BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
Dysbiosis test	GA-map™ Dysbiosis Test
FODMAP	Fermentable oligo-, di- and monosaccharides and polyols
GSRS-IBS	Gastrointestinal Symptom Rating Scale modified for use in patients with IBS
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhea
IBS+/MO+	Subjects with MO and IBS
IBS+/MO-	Subjects with IBS without MO
IBS-/MO+	Subjects without IBS with MO
IBS-/MO-	Subjects without IBS and without MO
IBS-SSS	Irritable bowel syndrome severity scoring system
LDL	Low-density lipoprotein
MO	Morbid obesity
MO-BiPS study	Morbid obesity and bio-psycho-social factors study
OR	Odds ratio
SSRI	Selective serotonine reuptake inhibitors

Background

Irritable bowel syndrome (IBS) and obesity are two common disorders with multifactorial etiologies [1-3]. The research project that this thesis arises from started in 2012 with the observation that many of the pathophysiological factors in IBS and morbid obesity (MO) were similar: Low-grade inflammation, dietary factors, mental distress and alterations of the microbiome have been reported to be associated with both disorders [4-11].

Irritable bowel syndrome

The main symptom of IBS is recurrent abdominal pain related to defecation [12]. IBS can lead to reduced quality of life, and is a cause of substantial health-related costs, mainly due to absence from work [5, 13]. Many comorbid conditions are associated with IBS, including pain syndromes and psychiatric disorders. IBS is caused by a combination of intestinal factors and psychological factors [13-15]. The gut microbiome and low-grade inflammation might be implicated in the pathogenesis [16-18] .

Diagnostics

IBS is diagnosed with the Rome questionnaires [12, 19]. As IBS is a symptom-based diagnosis, specificity has often been studied among patients with other

organic gastrointestinal disorders, and sensitivity among already diagnosed cases with IBS. Evaluated this way, the different iterations of the Rome questionnaires do have decent sensitivity and specificity [20, 21]. Reproducible biomarkers of IBS in blood or faeces that are easy to analyse and have high diagnostic accuracy have not been found despite extensive research [21, 22]. A biomarker with very high sensitivity and specificity could lead to better diagnostics, more precise epidemiological studies and selection of the right patients for studies of treatment. We wanted to study diagnostics of IBS because we together with collaborators in Oslo got the opportunity to test subjects with a promising new faecal biomarker.

Prevalence

IBS is a very common disorder that is most prevalent in women [1, 23]. Studies of IBS prevalence in different populations have been performed with the Rome criteria. A meta-analysis of studies that have examined IBS prevalence in general populations showed a worldwide prevalence rate of 11.2% (95% CI 9.8–12.8) [23]. A later literature review questioned whether a pooled global prevalence rate was appropriate, but presented a pooled prevalence of 7.1% (95% CI 6.0–8.3) in Europe, North America, Australia and New Zealand [1]. The epidemiology of a symptom-based disorder that tends to come and go is recognized as a tricky topic [24, 25]. When our study was planned, it was not

known whether IBS was more common in subjects with MO. Gastrointestinal comorbidity in subjects with MO is an important research topic as we currently treat these subjects with bariatric surgery, a treatment that can lead to considerable complications and side effects from the gut [26, 27]. We wanted to study IBS prevalence in subjects with MO because the literature on the topic was sparse and conflicting, while subjects with MO were readily available for recruitment in our new obesity unit at Innlandet Hospital Trust Gjøvik (Gjøvik) and at the obesity unit at Oslo University Hospital Aker (Aker).

Treatment

The treatment of IBS includes reassurance and explanation of the functional nature of the disorder. A recent management algorithm emphasizes the importance of establishing a strong patient-physician relationship. A first-line approach of healthy eating habits and increased physical activity may relieve IBS in some patients [28]. If reassurance and lifestyle interventions are insufficient, treatment based on the patient's predominant symptom should be added [28, 29]. Patients with diarrhea could use loperamide or psyllium [29]. Patients with constipation could use psyllium or laxatives [29]. For subjects with pain as the predominant symptom; peppermint oil, low dose tricyclic antidepressants or selective serotonine reuptake inhibitors (SSRI) are recommended [29]. Psychological treatments like psychotherapy, cognitive

behavioral therapy or meditation are effective in severe IBS [30, 31]. Tricyclic antidepressants and SSRIs could also be used for treatment of comorbid depression, anxiety and stress [29].

During the last ten years, new treatments of IBS have been discovered. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been shown to reduce symptoms [32]. Two new drugs have been approved in Norway for the specific indication IBS after successful phase 3 trials. Linaclotide (Constella®) is a minimally absorbed guanylate cyclase C agonist for IBS with constipation (IBS-C). Eluxadoline (Truberzi®) is a peripherally acting opiate based agent for IBS with diarrhoea (IBS-D) [3, 33]. However, there is limited direct evidence that these new drugs are superior to the older and cheaper treatments [28]. At the start of our project, we did not know whether IBS in subjects with morbid obesity responded to different treatment than IBS in normal weight individuals.

Obesity

Obesity is adipose tissue accumulation to an extent that increases disease risk [34]. Body mass index (BMI) is not a perfect measure of obesity but is the most commonly used both in clinical practice and research [2]. Subjects with a BMI above 25 kg/m^2 are defined as overweight and persons with a BMI above 30

kg/m^2 as obese. The health impact of obesity increases worldwide [35]. The prevalence of obesity is probably around 25% in adults in Norway [36]. There are several ways to delineate the most severe cases of obesity. In the three papers used in this thesis, we have used the term 'Morbid obesity' (MO). MO is diagnosed in subjects with a BMI above 40, or in subjects with a BMI above 35 and obesity-related complications [36]. MO is present in about 3% of the Norwegian population [37]. Obesity could be understood as a large number of overlapping pathophysiological entities that lead to excess adipose tissue accumulation [2, 38]. Processes in the hypothalamus are often of high importance in the aetiology of obesity [39]. As in IBS, the gut microbiome [40] or low-grade inflammation [9, 38] might be implicated in the pathophysiology.

Gastrointestinal comorbidities of obesity

Several gastrointestinal disorders as gallstones, cancer and liver disease have been associated with high BMI and considered as comorbidities of obesity [41]. Associations between obesity and functional gastrointestinal disorders have been shown in population-based studies for upper gastrointestinal disorders [42, 43], but also for functional bowel disorders as IBS [42, 44], bloating [43, 45] and diarrhoea [45]. Only a few small studies had investigated the relations between MO and IBS in adults before the start of our research project [46, 47].

Knowledge about whether weight loss leads to improvement of bowel symptoms was also limited [47, 48].

Pathophysiology

Low-grade inflammation

When cells in one part of a human body are injured, immune cells are recruited to the relevant tissue to repair the damage in a process that includes inflammation. An inflammation reaction can also overshoot and cause symptoms, tissue degradation and disease, as known from inflammatory bowel disorders or rheumatic disorders [49].

An inflammatory process in one part of a body can lead to elevated inflammatory markers as interleukins and C-reactive protein (CRP) in the systemic circulation. Low-grade systemic inflammation is present in a large proportion of subjects with obesity, and is visible on blood tests as slightly higher levels of inflammatory markers [2, 9, 50]. The levels of many inflammatory markers are reduced after reduction of adipose tissue by surgical or non-surgical methods [9, 51-53]. Parts of the systemic inflammation in subjects with obesity is probably caused by adipokines, cytokines secreted from adipose tissue [2].

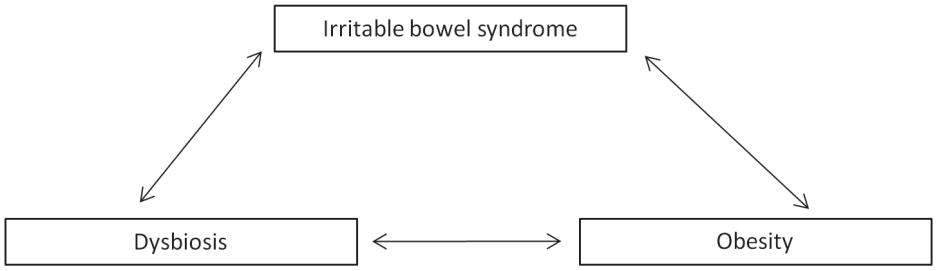
To what extent fat-mass-induced low-grade inflammation is causally related to the comorbidities of obesity is uncertain and an area of active

investigation [54]. IBS has often been discussed in relation to inflammation, and low-grade inflammation as a main cause of IBS in obesity has been proposed [55]. Some studies have shown associations between IBS and cytokine profiles in the serum [56]. Subjects with IBS have in some studies had slightly higher CRP values than healthy controls [7, 18].

Microbiome

In the last decade, we have seen considerable advances in genetic methods for the examination of the microbiota, all microorganisms that collectively inhabit an ecosystem. The microbiome is a term for all microbial genes present in an ecosystem [57]. The human faecal microbiome, which can be analysed from faeces without use of any endoscopic examination, can probably be used as a proxy for the microbiome of the human intestinal mucosa [58]. Changes in the faecal microbiota have been associated with many diseases, including IBS [16, 58-61] and obesity [40, 62-64]. Dysbiosis has been defined as a faecal microbiota pattern that 'differs from what is found in a healthy gut [65].'

Figure 1: Possible causal relations between IBS, obesity and dysbiosis



Which direction eventual causal relations between dysbiosis, obesity, and IBS go is not known. Hope that the new knowledge about the microbiota could lead to therapies in human beings is often expressed, but until now the evidence for this is limited [66-70].

Diet

Some diets will cause disease in almost all human beings (e.g., not eating any vitamin C at all), but usually, the effect of a diet on a disease also depends on other factors in the subject. Such factors could be differences in intestinal physiology due to variations in the genome or the intestinal microbiota [71]. The interactions can be quite straightforward and determined by one specific gene (lactose leads to diarrhoea and abdominal discomfort in adults who lack the allele that gives lactase persistence), but we expect many of these relations to be complicated with many different factors involved [57]. Dietary choices are probably an important part of the aetiology of both IBS and MO. Dietary

intervention is a part of the recommended treatment programs for both conditions [28, 34].

A majority of IBS patients experience that certain types of food trigger their gastrointestinal symptoms, local immune activation in the gut is probably one of the reasons for this [72-74]. The low FODMAP diet has gained attention and popularity in IBS even though the evidence behind it still is quite limited. Traditional IBS diets can give comparable results to a low FODMAP diet [75]. In obesity, there is a known relation between energy intake and weight. Very high or very low consumption of energy will lead to weight increase or weight loss. Sustainable weight loss induced by dietary changes is hard to achieve, with a limited long-term effect of low-calorie diets [34]. This might be due to the endocrine interplay between the gut and the hypothalamus, an exciting topic that is beyond the scope of this thesis [2, 39].

Mental distress

Psychological factors will also impact symptoms and disease in many different organ systems. Mental distress can lead to autonomous effects like high blood pressure and altered intestinal motility [76]. Long-term stress is also a risk factor and probably a cause of obesity [39]. That mental distress leads to higher storage of energy was a useful adaptation in evolutionary time but can be problematic in current societies with constant availability of energy-dense food.

Mental distress might be one reason why the most vulnerable in a society often have higher prevalence rates of obesity [76-78]. Anxiety, depression and stress have also been related to IBS through many different pathophysiological mechanisms [72].

Rationale for the thesis

IBS impacts the quality of life of many people, and further improvement of the treatment and biomarkers of this condition is needed. An understanding of why subjects with MO have a high prevalence of IBS could lead to important pathophysiological insights concerning IBS in general. Observational studies are also important preliminary work to find out how to treat patients with concurrent obesity and IBS.

Aims

Paramount aim: To study IBS in subjects with MO.

- Study the prevalence of IBS in subjects with MO

  Paper I.

- Study the predictors of IBS in subjects with MO.

  Paper I.

- Study the microbiome in subjects with and without MO and IBS.

  Paper II.

- Study changes in IBS symptoms during weight loss.

  Paper III.

Material and methods

Innlandet Hospital Trust provides secondary health care to about 400.000 people in Eastern Norway and has somatic departments at six different geographical locations. Some specialized treatments are centralized to one of these six locations. A centralized unit for treatment of MO at Innlandet Hospital Trust was established at Gjøvik in Oppland County in 2011, and bariatric sugery was performed at Gjøvik from April 2012. At this unit for treatment of MO, we included subjects to the MO-BiPS (Morbid obesity and bio-psycho-social factors) study from December 13th, 2012 through September 2014. This thesis is based on three scientific papers that all use data from the MO-BiPS study. In paper I and II, the collected data from the MO-BiPS study was combined with data collected by collaborating groups.

Table 1: Number of subjects included in paper I, II and III

Paper	Design	Collaboration with	Number of study subjects from MO-BiPS	Number of study subjects from other groups
I	Cross-sectional study	Oslo University Hospital, Aker	139	211
II	Cross-sectional study	Lovisenberg Diaconal hospital	99	63
III	Prospective cohort study	n.a.	88	

Design

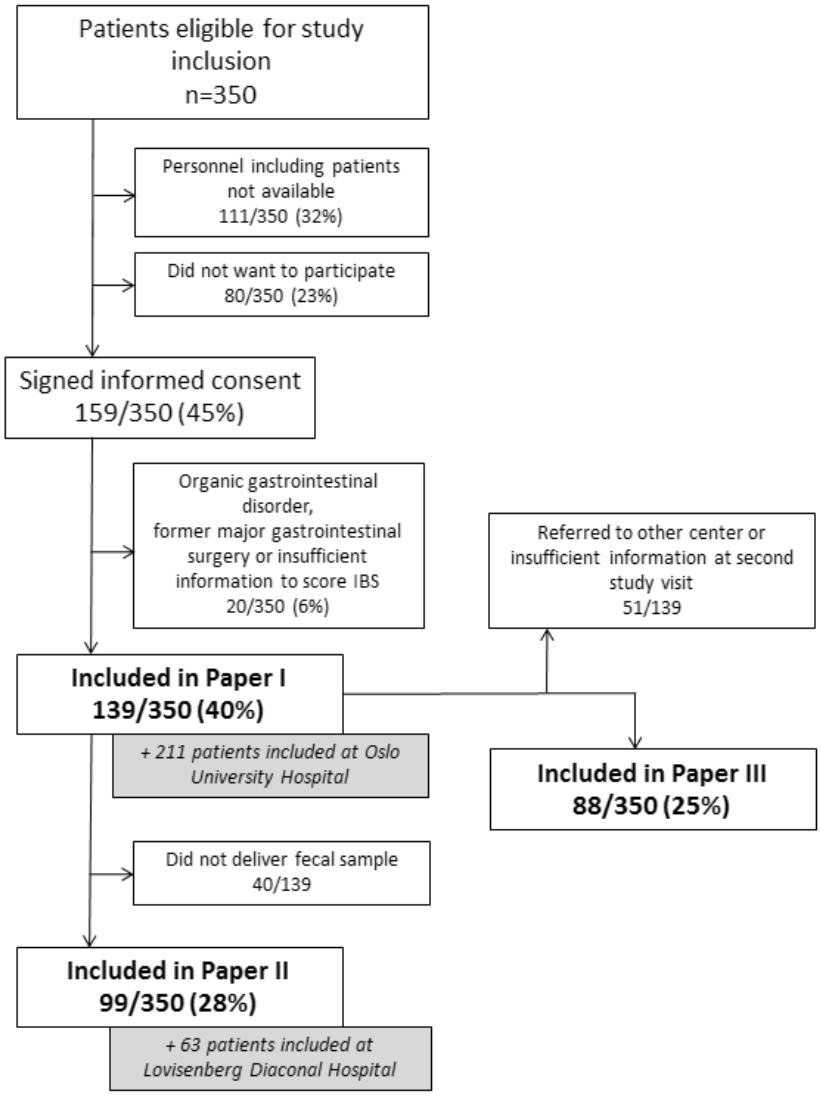
Paper I was a cross-sectional study that included subjects from the MO-BiPS study and subjects from a comparable clinic for MO at Aker. In this paper, we examined the prevalence and predictors of IBS based on data from questionnaires and blood tests.

Paper II was a cross-sectional study that included subjects from the MO-BiPS study and subjects from a gastroenterological outpatient clinic at Lovisenberg Diaconal Hospital. In this study, we examined the relations between IBS, obesity, and dysbiosis based on data from questionnaires and a faecal test.

Paper III was a prospective cohort study that only included subjects from the MO-BiPS study. In this study, we examined changes in IBS symptoms and symptoms of other functional gastrointestinal disorders during a conservative weight loss intervention, based on data from questionnaires and blood tests.

Participants

Figure 2: Inclusion of subjects to paper I, II and III



The figure shows all subjects with morbid obesity seen for the first time at the obesity clinic at Innlandet Hospital Trust Gjøvik from December 13th 2012 through September 2014.

Subjects referred to the obesity centre at Innlandet Hospital Trust Gjøvik were asked about inclusion in the MO-BiPS study. All 350 subjects who had their first appointment at the centre in this period were informed that research was going on in the section for MO, and were given an informed consent form to read through. If the subject accepted inclusion and the research nurse responsible for storage of material was available, the subject was included. One hundred and eleven out of 350 (32%) were not included because they arrived on days when the research nurse was not available (she only worked part-time). Eighty out of 350 (23%) did not want to participate for various reasons, often due to time constraints. The 159 subjects who wished to participate were given a case report form (Appendix 4) and a food frequency questionnaire for nutritional registration [47]. They were asked to meet fasting to have blood drawn, and were given sampling kits for urine and faeces to bring back at the next visit to the hospital.

The inclusion and exclusion criteria to the MO-BiPS study were similar to the referral criteria to the obesity centre. We included subjects who had MO and age between 20 and 65 years. MO was defined as either BMI >40 kg/m² or BMI >35 kg/m² with complications (diabetes mellitus, hypertension, sleep apnoea, respiratory failure or musculoskeletal pain related to movement) at the time of referral [23]. Exclusion criteria for the main MO-BiPS study were major psychiatric disorders, alcohol and drug addiction.

The different papers based on the MO-BiPS study had additional exclusion criteria. In all three papers used in this thesis, we excluded subjects with organic gastrointestinal disorders and subjects where we had insufficient information to score IBS at the first study visit (Figure 2). Paper II did also exclude subjects that did not deliver a faecal sample. Paper III excluded subjects that did not undergo the conservative weight loss program at Innlandet Hospital Trust Gjøvik, and subjects with insufficient information to score IBS at the second study visit.

Questionnaires about bowel symptoms

Rome III criteria The Rome III criteria, current at the time of inclusion to the study, were used to diagnose functional bowel disorders [12]. IBS including subtypes (IBS-constipation, IBS-diarrhoea, IBS-mixed and unsubtyped IBS), functional bloating, functional constipation and functional diarrhea were evaluated as present or absent.

Irritable bowel syndrome severity scoring system (IBS-SSS). The IBS-SSS is a scoring system developed for use in clinical and research settings. The score ranges from 0 to 500, high scores indicate higher severity. Mild, moderate and severe cases can be defined by scores of 75 to 175, 175 to 300 and >300 respectively. Subjects with IBS with a score below 75 can be considered to be in remission [79]. A change of 50 is clinically significant [75].

Gastrointestinal Symptom Rating Scale modified for use in patients with IBS (GSRS-IBS). The GSRS-IBS is a scoring system created to derive an IBS-specific version of the GSRS questionnaire [80]. The scale has five subscales : Pain syndrome, bloating syndrome, constipation syndrome, diarrhoea syndrome and satiety. The score and the subscales were used with ranges from 1 to 7, high values indicate discomfort. The GSRS-IBS score is based on 13 questions that all use the same response scale: 1 = No discomfort at all, 2 = Minor discomfort, 3 = Mild discomfort, 4 = Moderate discomfort, 5 = Moderately severe discomfort, 6 = Severe discomfort, and 7 = Very severe discomfort.

Other questionnaires about health

Table 2: Questionnaires used in the MO-BiPS study

	Measures	High values indicate	Range
Hopkins Symptom Checklist 10 [81]	Psychological distress/mental health problems	Psychological distress	1-4
WHO-5 Well-Being Index [82]	Emotional well-being	High well-being	0-100
Rosenberg's Self-Esteem Scale [83]	General self-esteem	High self-esteem	1-4
Fatigue Severity Scale [84]	Fatigue	High level of fatigue	1-7
Epworth Sleepiness Scale [85]	General daytime sleepiness	High sleepiness	0-24
Sense of Humour Questionnaire [86]	Sense of humour	High sense of humour	1-4
Suter's Questionnaire [87]	Food tolerance	Good food tolerance	1-27
Musculoskeletal pain score	Degree of musculoskeletal pain	More pain	0-12
Physical activity score	Spare time physical activity	High levels of physical activity	0-8

Questionnaire about diet

The intake of macronutrients and micronutrients was estimated with a semi-quantitative food frequency questionnaire created and validated for the Norwegian population [88].

Blood tests

Table 3: Blood tests from the MO-BiPS biobank

	Used paper I	Used paper III	Analysed
Haemoglobin	X		Gjøvik
White-cell count	X		Gjøvik
Platelet count	X		Gjøvik
C-reactive protein (CRP)	X	X	Gjøvik
Cholesterol	X	X	Gjøvik
High-density lipoprotein	X	X	Gjøvik
Low-density lipoprotein (LDL)	X	X	Gjøvik
Thyroid stimulating hormone	X	X	Gjøvik
Free thyroxin	X	X	Gjøvik
Vitamin B_1	X	X	Aker
Vitamin B_6	X	X	Aker
Vitamin B_{12}	X	X	Gjøvik
Vitamin D		X	Gjøvik
Folic acid	X		Gjøvik
HbA1c	X	X	Gjøvik
Total bilirubin	X		Gjøvik
Mean corpuscular volume	X		Gjøvik
Mean corpuscular hemoglobin	X		Gjøvik
Iron	X		Gjøvik
Transferrin	X		Gjøvik
Transferrin saturation	X		Gjøvik
Ferritin	X		Gjøvik
Transferrin iron binding capacity	X		Gjøvik
Sodium	X		Gjøvik
Potassium	X		Gjøvik
Magnesium	X		Gjøvik
Phosphate	X		Gjøvik

Glucose	X	Gjøvik
Creatinine	X	Gjøvik
Uric acid	X	Gjøvik
Alanine aminotransferase	X	Gjøvik
Total protein	X	Gjøvik
Albumin	X	Gjøvik
Triglycerides	X	Gjøvik

Faeces tests

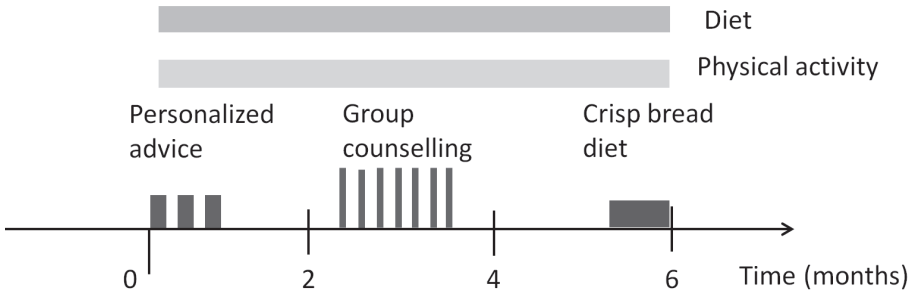
The microbiome was assessed with GA-map^{TM} Dysbiosis Test (dysbiosis test), a test of genetic material from faeces that has been invented, produced and marketed by Genetic Analysis, Oslo, Norway. The dysbiosis test is CE-marked and is based on a panel of 54 nucleotide probes that could separate IBS patients from healthy control subjects [89]. These 54 probes target variable regions (V3 to V7) of the bacterial 16S rRNA gene. During creation of the test, the probes were selected from a dataset of 496 16S rRNA sequences that had been associated with IBS and IBD in earlier microbiota research [89]. The dysbiosis test was therefore based on less, but more targeted information than what is examined during traditional 16S rRNA exploration of a microbiome [57, 90].

The faecal material was collected by the included subjects in kits provided by the producer and was handled according to the producer's protocol. Analysis of the faecal tests was done at the producer's own laboratory in Oslo, and the producer was blinded to all phenotypic information about the subjects.

Results were delivered back to our research group as a score on a dysbiosis index (ranging from 1-5), where high scores indicated more severe dysbiosis and scores ≤ 2 indicated no dysbiosis.

Interventions

Figure 3: Components of the conservative weight loss intervention



Paper III presented data collected before and after a conservative weight loss intervention. The weight loss intervention lasted for six months, was based on a series of outpatient visits and consisted of many different components (Figure 3). The same six month period was also the run-in period before bariatric surgery. The intervention was comparable to weight loss programs used in other Norwegian hospitals [91]. Some local changes were done based on the availability of personnel at Innlandet Hospital Trust. All included subjects started the period with personalized advice offered by three different health professionals; a nurse, a nutritionist and a doctor in internal medicine. After some months where the subjects were expected to implement the advice, the

next main element was group counseling, where the subjects worked together with 17-19 other subjects with the same health problem. In the last weeks of the weight loss intervention, the subjects ate a crisp bread diet or meal replacement powder. The subjects were told that a high weight loss (>10%) in the conservative weight loss period could lead to fewer complications after surgery, and that their weight loss in the conservative period would partly decide whether they would be accepted for bariatric surgery by the responsible surgeon.

Ethics

The MO-BiPS study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway with reference 2012/966 and was conducted following the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Health information was given by the subjects written by pen on paper-based case report forms. These original case report forms were archived according to national regulations. The link between study numbers and the national identification numbers of the subjects was archived separately. Information from paper was transferred to a computer manually in the hospital. All resulting digital files are kept on a server with security according to rules by the Norwegian Data Protection Authority, P.O. Box 8177 Dep. NO-0034 Oslo,

Norway. Subjects were welcome to withdraw from the study whenever they wanted.

Statistics

Software

The statistical analyses were mainly performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp). A few analyses not available in the SPSS package were performed with Stata Statistical Software, Release 13 (College Station, TX: StataCorp LP) and in R (Vienna, Austria: R Foundation for Statistical Computing).

Sample size calculation

The sample size calculation for the whole MO-BiPS project was done based on some planned substudies. One of these substudies concerned change in IBS after bariatric surgery. Based on an expected reduction in the prevalence of IBS from 18% to 9% (11% get rid of IBS after surgery, and 2% without IBS get symptoms after surgery), with $\alpha = 0.05$ and power $(1-\beta) = 0.80$ we calculated that we needed a sample size of 100 subjects. The original plan was therefore to include 100-120 subjects, which was the number of patients operated during one year. Observation of dropout between inclusion and the second and third control led us to increase the inclusion to 159 subjects. The workload for the

study nurse and subsequent loss to follow-up when inclusion and follow-up were going on in parallel was the main reason to stop inclusion in September 2014. We wanted to use our resources on follow-up of already included subjects and handling of biobank material.

We did also do a sample size calculation for paper I. The prevalence of IBS was 8.4% in the general population from the same area and was expected to be 18% in subjects with MO [5, 46]. A study with 350 participants with MO was calculated to have a power of 98% to detect a difference between the general population and the subjects with MO, with $\alpha = 0.01$.

Missing data

Subjects with missing data to an extent that made it impossible to score IBS according to the Rome III criteria were excluded from the studies as presented in the methods sections of the papers. Missing data on other functional bowel disorders, comorbidities or blood tests were reported in the tables as a reduced n. Missing data were handled using available case analyses, that is, in each analysis the cases with data on the relevant variables were used. Available case analysis was judged as acceptable as the ratio of missing data was low, with 0-6 missing numbers (<6%) for each variable in paper 1, and 0-7 missing numbers for each variable in paper 3 (<10%).

Post hoc analysis

The large difference in IBS prevalence between the two centres in paper I made post hoc analysis desirable. We therefore also compared subjects with and without IBS separately at the two centres (Table 3 in paper I). This was not part of the original analysis plan, and the analyses were described as post hoc in the paper. A reviewer of paper III suggested stratified analysis because of the large difference between changes in subjects with and without IBS. We did as the reviewer suggested, and included this post hoc analysis as table 4 in paper III.

Processing of variables

The different case report forms at Gjøvik and Aker led to some processing of variables before the analyses. At Gjøvik, subjects were asked about a history of any minor psychiatric disease (anxiety or depression). At Aker, the subjects were given two questions about this topic, one about anxiety and one about depression. We did merge the answers to these questions to a common variable 'self-reported psychiatric disease.' Subjects at Gjøvik with 'yes' to minor psychiatric disease, subjects at Aker with 'yes' to anxiety and subjects at Aker with 'yes' to depression were all given the value 'yes' for the new variable 'self-reported psychiatric disease.' At Gjøvik, subjects were asked about fibromyalgia/chronic pain syndrome. At Aker subjects were only asked about

fibromyalgia. ‘Yes’ on these two questions were also merged to a common variable called ‘fibromyalgia.’

Analyses

Comparisons of continuous variables in two independent groups were made with the unpaired *t*-test or the Mann-Whitney *U* test, depending on the distribution of the variable. For categorical variables in two independent groups, Chi-squared test or Fisher’s exact test were used. For correlation between two continuous variables, the Pearson correlation coefficient or Spearman’s rank correlation coefficient were used according to the distribution of the variables. We used logistic regression for analysis of the relation between one dichotomous dependent variable and several explanatory variables. Linear regression was used for analysis of the relation between one continuous dependent variable and explanatory variables. Analysis of variance was used to compare continuous, normally distributed variables in three or four groups. Kruskal-Wallis test was used as the non-parametric alternative to analysis of variance.

Comparisons of continuous variables in two paired groups were made with paired t-test or Wilcoxon signed-rank test depending on the distribution of the data. McNemar’s Test was used on paired categorical data.

A two-sided p-value <0.05 was considered statistically significant, and 95% confidence intervals (CI) are reported where relevant.

Table 4: The statistical methods used

	Paper I	Paper II	Paper III
Unpaired *t*-test	Yes	Yes	
Mann-Whitney *U* test	Yes		
Pearson chi-squared test	Yes	Yes	
Fisher's exact test	Yes	Yes	
Pearson correlation coefficient	Yes		
Spearman's rank correlation coefficient	Yes		
Logistic regression	Yes	Yes	
Newcombe 95% confidence interval			Yes
McNemar's Test			Yes
Wilcoxon signed-rank test			Yes
Paired *t*-test			Yes
Stuart-Maxwell test			Yes
Linear regression			Yes
One-way analysis of variance		Yes	
Kruskal-Wallis test		Yes	
Reciever operating characteristic curve		Yes	

Correction for multiple testing

In paper I, no correction for multiple testing was performed, but full information about the total number of predictors that were examined was

provided. Two of the predictors identified in paper I had p-values that would have remained significant after Bonferroni correction. In paper II, the analysis only focused on one variable, dysbiosis (yes/no), and correction for multiple testing was not judged to be relevant. In paper III, correction for multiple testing was performed with Benjamini-Hochberg False Discovery Rate in the final analysis.

In microbiome research and inflammation research, correction for multiple testing is often relevant. Transparency about whether aims were chosen before the study was performed is arguably also critical, as the number of potential hypotheses that could be examined is enormous. Many published exciting associations expected to have biological significance have not been reproduced. One reason for this could be publication bias, where positive findings are more likely to be published, or storytelling bias, where positive associations identified in a large data material with many variables are more likely to be worked into a story in an abstract and manuscript and subsequently published.

Evaluation of a diagnostic test

In the assessment of the dysbiosis test as a diagnostic test, we defined four groups of subjects: Subjects with MO and IBS (IBS+/MO+), subjects with IBS without MO (IBS+/MO-), subjects with MO without IBS (IBS-/MO+) and

subjects without MO and without IBS (IBS-/MO-). Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated, considering the dysbiosis test as a diagnostic test for IBS in subjects with MO and subjects without MO. A receiver operating characteristics curve was calculated to illustrate the diagnostic ability of the dysbiosis test.

Summary of results

Study the prevalence and predictors of IBS in subjects with MO

The prevalence of IBS was 54/350 (15%) among all included subjects. The prevalence varied widely between two obesity centres as it was 17/211 (8%) at Aker and 37/139 (27%) at Gjøvik. This meant that the IBS prevalence in subjects with MO at Aker was comparable to the IBS prevalence in the general Norwegian population, while the IBS prevalence in subjects with MO at Gjøvik was threefold higher.

High low-density lipoprotein (LDL) (OR 2.10; 95% CI 1.34-3.29), self-reported psychiatric disorders (OR 2.39; 95% CI 1.12-5.08) and centre (OR 5.22; 95% CI 2.48-10.99) were independent predictors of IBS.

Study the microbiome in subjects with and without MO and IBS

The prevalence rates of dysbiosis in the groups IBS+/MO+, IBS-/MO+, IBS+/MO-, and IBS-/MO-, were 18/28 (64%), 45/71 (63%), 31/63 (49%) and 38/91 (42%). Dysbiosis was more common in subjects with MO than in subjects without MO, there were no significant differences in dysbiosis prevalence between subjects with and without IBS.

Study changes in IBS symptoms during weight loss

During weight loss, we saw a significant improvement in a majority of all measured variables. IBS-SSS was reduced from 116 (104) to 81 (84), p=0.001, while GSRS-IBS was reduced from 1.8 (0.8) to 1.6 (0.6), p=0.006. Subjects with IBS before the intervention had an IBS-SSS improvement of 88 (95% CI 55 to 121). Improved bowel symptoms were associated with improvement in subjective well-being, sense of humour and vitamin D, and negatively associated with improvement in BMI.

General discussion

Our first aim was to study the prevalence of IBS in subjects with MO. The substantial difference in IBS prevalence between the two obesity clinics could have been due to differences between the populations living in the urban and the rural areas. Other studies of IBS in MO published between 2003 and 2018 did also show considerable variation in prevalence rates (Table 5).

Table 5: Prevalence of IBS in subjects with MO, other studies

	Criteria	Prevalence	Recruited at
Published before inclusion to the MO-BiPS study			
Foster 2003 [47]	Unspecified	7/43 (16%)	Obesity clinic
Fysekidis 2012 [46]	Rome III	22/120 (18%)	Obesity clinic
Published during the MO-BiPS study			
Santonicola 2013 [92]	Rome III	12/100 (12%)	Obesity clinic
Bouchoucha 2015 [93]	Rome III	33/360 (9%)	Obesity clinic
Bouchoucha 2015 [93]	Rome III	16/51 (31%)	Gastroenterological outpatient clinic
Schneck 2015 [94]	Rome III	30/100 (30%)	Obesity clinic
Le Pluart 2015 [95]	Rome III	Around 6%	Volunteers
Bouchoucha 2016 [96]	Rome III	4/51 (8%)	Gastroenterological outpatient clinic
Andalib 2018 [97]	Manning	113/378 (30%)	Obesity clinic

A study of consecutive patients with MO seen at a French gastroenterological outpatient clinic showed a high prevalence of IBS [93]. This was expected as these subjects were referred for gastrointestinal complaints. Some groups of subjects with MO referred for obesity treatment have had lower prevalence rates of IBS [46, 93, 96]. Based on these observations *Bouchoucha et al* stressed the importance of the enrolment source: The prevalence of IBS depends on what the included subjects are referred for [93]. This explains some of the variation seen in table 5 and could also explain an association found in children [98] but can not explain either the high prevalence observed in the study by *Schneck et al* [94], the high prevalence in our study population from Gjøvik [99] or the association between IBS and obesity seen in previous population-based studies [42, 44].

In a review of the global prevalence of IBS in adults the conclusion was that *'the main finding is the extent of methodological variance in the studies reviewed and the degree of heterogeneity among them*.' The authors stated that the global prevalence of IBS remains elusive [1]. Our current conclusion about the relation between IBS and MO can be expressed in a similar way. Whether IBS should be considered as a general comorbidity of obesity remains unclear due to the heterogeneity of study designs and populations examined. Based on our study [99] and other research (Table 5), we could conclude that IBS is very common in some groups of subjects with MO.

Why is IBS very common in some groups of subjects with MO? The threefold difference in IBS prevalence between the two centres in our paper I could be used to explore this question. Whether this difference was due to error in our research methods was carefully evaluated. Random error as a single explanation was unlikely given the numbers of subjects included and the size of the difference between the two centres (e.g., chi-square test $p = 0.0001$). Systematic error or bias is divided into two main categories, information bias, and selection bias. Concerning information bias, the Rome III questionnaires had the same wording at the two centres and were at both centres filled out by the subject after a clinical consultation. A difference that could have led to information bias was that some of the questionnaires given in the case report form before the Rome III questionnaire were different at the two centres (Aker: About abdominal pain, Gjøvik: About food intolerance). Some subjects' answers about 'recurrent pain or discomfort' in the Rome III questionnaire could have been affected by whether they answered questions about pain or food intolerance just before.

Selection bias in paper I could be considered at two levels; (I) Were the included subjects representative of all subjects with MO referred to the hospital? and (II) Were the included subjects representative of all subjects with MO in the region? At level I, the inclusion percentage meant that even if none of the non-included subjects at Gjøvik had IBS (Figure 2), the prevalence of

IBS at this centre would still be quite high 37/239, 15.4%. At level II, the problem of selection bias could have been large if the referral practice varied a lot between the regions, as the percentage of all subjects with MO referred to obesity centres in the study period only was about 5% [37]. However, the criteria for referral were identical at Aker and Gjøvik, and almost all referred subjects were accepted to the outpatient clinics in the inclusion periods. We do not know whether the subjects with MO in the urban area had undergone more or less treatment than the subjects with MO in the rural areas before referral to the obesity clinic.

IBS is due to interplay between peripheral gut factors and central psychological factors, and mental distress could also affect the actual symptom load of an IBS patient (not only lead to information bias) [72]. The impact of being in slightly different phases of the treatment program should therefore be considered: The subjects included at Gjøvik did not know whether they would get bariatric surgery, while the subjects included at Aker were included at a moment when they knew that they would be offered bariatric surgery. A potential life-changing event that is undecided might have had an impact on mental distress and thereby on bowel symptoms. 'Knowledge about the bariatric surgery decision' could, therefore, be considered as a source of systematic error if what we wanted to study was the association between region of residence and IBS. Furthermore, it is possible that the subjects included at

Aker had changed their diet more at the time of the intervention. We know from the results in paper 3 that a conservative weight loss intervention has an impact on bowel symptoms.

Our second aim with paper I was to identify independent risk factors, predictors of IBS among subjects with MO. Based on previous research and reviews, mental distress, diet, fat-mass induced inflammation and the microbiome were elements that we wanted to explore [4, 7, 11, 17, 100, 101]. Microbiome analysis was not included in paper I because faecal samples were not available from the subjects included at Aker.

Concerning mental distress, we found an anticipated association between IBS and self-reported anxiety and depression, even though the subjects with major psychiatric disease were excluded. High prevalence rates of mental distress and psychiatric diseases in subjects with MO may be a partial reason for the high prevalence of IBS in some groups of subjects with MO. There have been speculations that subjects with MO and IBS have an unhealthy diet that both has led to bowel symptoms and obesity [101]. We found that high LDL in the blood was associated with IBS. LDL levels are known to be higher in periods with high energy intake than in periods with low energy intake. LDL could be considered as a biomarker of a diet rich in fats and simple carbohydrates [102]. We did observe that levels of LDL were higher at Gjøvik, the centre with the high prevalence of IBS. An unhealthy diet might be a main

cause of IBS in some of the subjects. Many subjects with IBS report gastrointestinal symptoms after intake of fried and fatty foods [73]. If an unhealthy diet is more common among the rural residents, this might also explain parts of the prevalence difference between the centres.

Low vitamin levels could also be considered as indicators of an unhealthy diet [103]. We did not find significant associations between IBS and serum vitamin levels in the final analyses, but levels of vitamin B_1 were lower in subjects with IBS than in subjects without IBS at both centres.

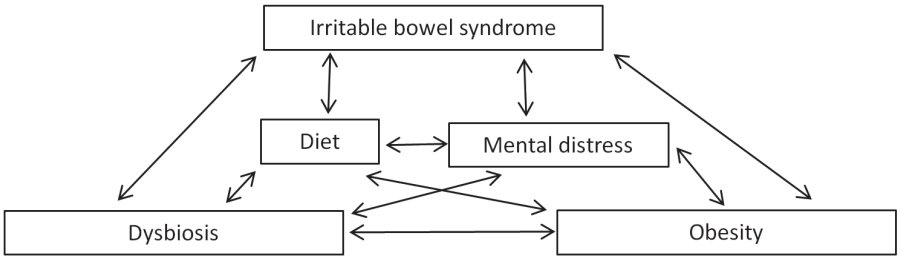
Our investigation of the inflammation hypothesis was focused on CRP. In the MO-BiPS study, CRP was not associated with IBS. We are aware that a larger panel of inflammatory markers might have given other results, and that local gut inflammation is more plausible than systemic low-grade inflammation as a contributing cause of IBS in MO.

Paper 1 had several limitations. The research projects in Gjøvik and at Aker started separately of each other. Therefore, registrations of comorbidity and symptoms with questionnaires were done in slightly different ways at the two centres. Additionally, routine blood tests were performed at two different laboratories. These differences limited the possibility to directly compare values between subjects included at Aker and subjects included in Gjøvik.

We chose to adjust all analyses of predictors for the centre in logistic regression analysis: The differences in measurement methods combined with

the large prevalence difference for IBS between the centres led to a large risk of systematic errors in direct comparisons between all subjects with IBS and all subjects without IBS. Even if the results of the blood tests and some comorbid conditions could not be directly compared between the centres, this was expected to make conclusions about relations between predictors and outcomes valid.

Figure 4: Relations between IBS, dysbiosis and obesity after paper I



Graph depicting relations between some of the factors of interest after consideration of the findings from paper I.

The data presented in paper I and other research published while we worked on the MO-BiPS study indicated that diet and mental distress were factors associated with IBS in MO. Both diet and mental distress could be causes of IBS, but the relations could also go in other directions. A graph visualizing some of the many possibilities is given as figure 4. Dysbiosis could be

associated both with IBS, obesity, diet and mental distress [11, 40], and emerged as an attractive next variable to explore.

In paper 2, we studied dysbiosis. We did not find an association between dysbiosis and IBS status in the MO-BiPS study. This contrasts to many other publications that have found different microbiota in subjects with and without IBS [16, 58, 59, 89]. The dysbiosis test was created by identification of probes that could separate subjects with and without IBS. Therefore, it surprised us that we found a similar prevalence of dysbiosis in subjects with IBS and subjects without IBS in the MO-BiPS study.

We evaluated several possible reasons for these surprising microbiome findings. A random error can never be totally excluded as an explanation, but the numbers of included subjects were reasonable and random error was judged unlikely as a single explanation. The dysbiosis test was performed by the same laboratory that had created the test, and no warnings about problems in the laboratory were given. Large laboratory errors were therefore not a probable explanation. IBS was diagnosed by the established Rome III criteria, double checked by two investigators and should be correct.

One probable explanation for the microbiome results could be problems with the dysbiosis test in subjects with obesity. IBS in the obese might be associated with other bacteria than IBS in lean subjects, and this could explain

why a dysbiosis test created by studies of normal weight subjects was not associated with IBS in obesity.

Another possible explanation for the surprising microbiome results could be problems with the external validity of the dysbiosis test. During the last five years, several confounding factors strongly associated with the microbiome have been identified, including but not restricted to diet, medication and stool composition [104, 105]. It is possible that microbiome patterns associated with IBS are so different in different geographical regions that it is tough to create a test that is reproducible in different populations.

Our samples from lean people were all from subjects with IBS, and we ended up comparing these data with all published material with the dysbiosis test in healthy subjects, which is an approach with limitations. A table of these published materials is nevertheless an interesting background for reflection and discussion (Table 5).

Table 6: Dysbiosis test in healthy controls

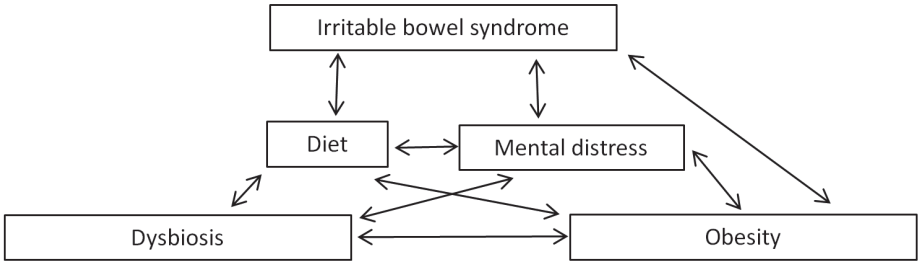
	Prevalence of dysbiosis	Comment
Casen 2015 I [89] Validation set	16% (7/43)	Among the 211 healthy individuals used in the creation of the test. Not used in paper II.
Casen 2015 II [89] Available samples from Denmark and Spain	40% (17/43)	Used in paper II.
Strindmo 2016 [106]	16% (7/43)	Identical to Casen I both in dysbiosis and dysbiosis index, this is the same 43 tests used doing the creation of the test. Not used in paper II.
Ricanek 2016 [107]	44% (21/48)	Used in paper II.

Healthy volunteers tested for faecal dysbiosis with the GA-map™ dysbiosis test, studies published until 30th of June 2017.

Dysbiosis was more common in subjects with MO than in subjects without MO. This is in accordance with other publications [40, 108]. Studies with many different methods have found a different microbiome in subjects with obesity, but the exact difference reported varies. Altered ratio of *Bacteroidetes* to *Firmicutes* and lowered microbiome diversity in the obese were often mentioned in 2013-2018 [64, 109, 110], but as reviewed by *Sze and Schloss* this has not been consistently reproduced [62, 108]. The associations between the microbiome and obesity might be weaker and less reproducible

than initially expected [62]. If we consider that the dysbiosis boxes in the figures represent dysbiosis as measured by this specific dysbiosis test, the arrows between IBS and dysbiosis could be removed after paper II.

Figure 5: Relations between IBS, dysbiosis and obesity after paper II



Graph depicting relations between some of the factors of interest after consideration of the findings from paper 1 and paper 2.

The fourth and last aim of the project was to study changes in IBS symptoms during weight loss. Weight reduction in human beings can be achieved with surgical methods or with non-surgical methods [34, 111]. The literature on non-surgical weight loss interventions in subjects with functional bowel disorders is sparse. A study of 17 patients did show that a very-low carbohydrate diet improved symptoms in IBS-D [48]. We are not aware of large studies that have evaluated the impact of conservative weight loss intervention on functional bowel disorders.

Concerning surgical weight loss, one small prospective study that evaluated gastrointestinal symptoms before and after surgical weight loss showed a reduction in IBS symptoms [47]. Another larger study showed high prevalence rates of IBS after surgery but the researchers did not have data on the same subjects before surgery [26]. Most kinds of surgery can lead to post-operative pain, and gastric bypass does not appear to be an exception [27]. Pain is a central symptom of IBS [12]. Therefore, bariatric surgery is a problematic model if it is the effect of weight loss on IBS that we want to examine.

Many positive life changes occurred at the same time for the 88 subjects included in paper III. Their social network was extended, they altered their diet and they on average lost ten kg of weight. Our primary aim was to compare bowel symptoms and IBS before and after the intervention. The main bowel symptom variables; IBS-SSS and GSRS-IBS, both changed significantly in the healthy direction. The prevalence of IBS was also reduced, though not significantly. Subscales of GSRS-IBS showed a significant improvement in bloating, diarrhoea and satiety, a significant worsening in constipation but no significant change in pain.

In paper 3, we also explored associations between changes in bowel symptoms and changes in the other variables with linear regression. As reported in the paper, four of the non-adjusted p-values were below 0.05: Improved IBS-SSS was associated with high improvement in the sense of humour and a low

improvement in BMI. Improved GSRS-IBS was associated with improvement in well-being and improvement in vitamin D levels.

Some other patterns in the correlations in paper 3 may also be worth noting, even though they did not reach significance and were kept out of the discussion in the paper. There were weak correlations between improvement in IBS-SSS and improvement in well-being and self-esteem. Improvement in GSRS-IBS was weakly correlated with improved sense of humour and improved psychological distress, and weakly correlated with improvements in cholesterol, vitamin B_1, vitamin B_6 and vitamin B_{12}. We concluded that 'psychosocial changes and possibly a more healthy and regular diet could explain the improvement in bowel symptoms.' None of the q-values after adjustment for multiple testing were significant, and all the findings in the final table in paper 3 should be considered as hypothesis-generating.

Table 7: Differences between the two study visits

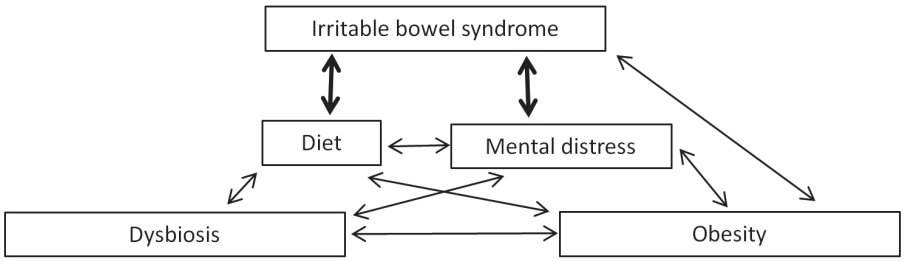
	Psychosocial setting	Diet the last weeks	Diet the same day
Study visit 1	New at the obesity clinic Do not know whether they will get bariatric surgery	Outpatient individuals Many have started a process where they change their diet, but large variation	Asked to be fasting Some subjects were possibly not fasting (high triglycerides observed)
Study visit 2	Bariatric surgery is confirmed One week before bariatric surgery	Crisp-bread diet and meal replacement powder	Fasting

Paper III is the only paper in this thesis that only uses data from the MO-BiPS study. It is also the only paper that is prospective and not cross-sectional. Changes between two time points could have been due to biological changes in the included subjects, but could also for instance be due to information bias at time point 1 or 2. Variables measured with questionnaires might be affected by cognitive biases [112]. Some blood tests might have been strongly affected by whether all subjects are fasting. Some of the known differences between the two time points are given as table 7.

The external validity of paper III could also be questioned. As many as fifty-one subjects provided all information at the first study visit but did not undergo the conservative weight loss program or provided insufficient information at the second study visit (Figure 2). The subjects who remained in

the study might have been a group with a high capacity for life change, and the effects among the included subjects could, therefore, be larger than what we would have seen in a group subjects with MO with no loss to follow up.

Figure 6: Relations between IBS, dysbiosis and obesity after paper III



Graph depicting relations between some of the factors of interest after consideration of the findings from paper I, II and III.

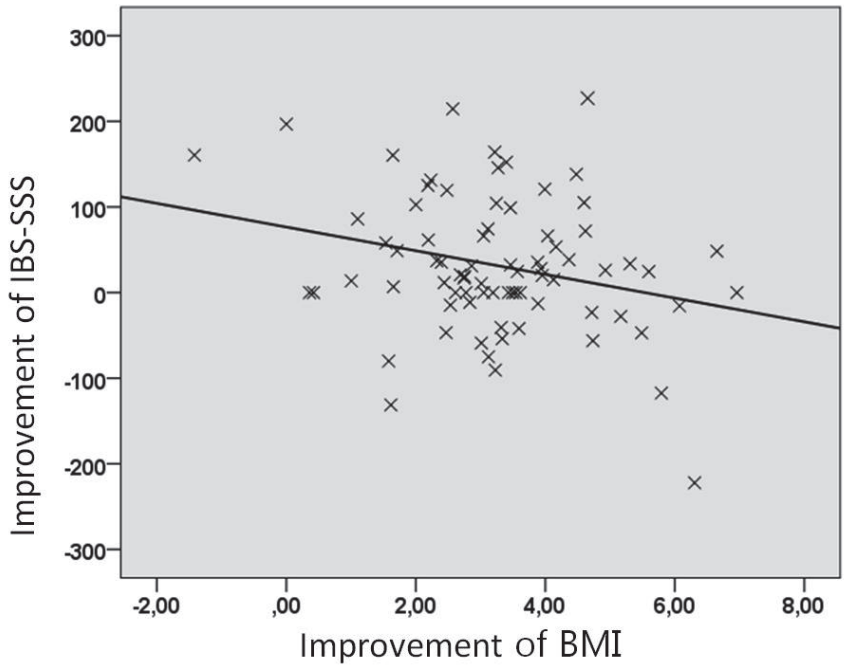
After consideration of the results from all the three papers included in the thesis and reading of other research published in the same time period, my simplified visualization of some of the relations was as given in figure 6. Diet and mental distress were at the centre of attention and did both have bold arrows linking them with IBS.

Research from the last five years has shown that IBS is very common in some groups of subjects with MO [94, 97, 99]. Whether the reason for this might be that MO causes IBS, that IBS causes MO, or that a third factor causes

both IBS and MO is hard to determine. However, one arrow that is biologically necessary is the arrow from MO to the diet. Subjects with MO will have to eat more than individuals with low body weight just to keep their body mass constant [2]. Overload of the digestive capacity can lead to bowel symptoms, as known from lactase deficiency or pancreatic insufficiency. Huge meals, where large quantities of food are eaten can lead to undigested molecules passing down to the large bowel, causing an increased osmotic load in the colon and symptoms as discomfort and diarrhoea [101]. The two IBS subtypes we saw most of in our study were the ones with diarrhoea: IBS-D and mixed IBS. MO might in some of the subjects be a pathophysiological situation where the capacity of digestion is too low compared to the energy needs of the body (energy-needing tissue has grown more than the gut). These subjects might eat meals of a size that give them bowel discomfort. This could explain the association between LDL and IBS (the subjects who eat most overload their digestion capacity and get symptoms). It could also explain the difference between the two obesity centres, given that the subjects recruited at Aker may have altered their diet more at the date of inclusion as they were examined at a later stage of their obesity treatment program. An association between binge eating and IBS or between LDL and IBS has also been observed in other studies [113, 114]. However, it is hard to see how the binge eating explanation fits with

the inverse relation between improvements in IBS and improvements in BMI shown in paper III (Figure 7).

Figure 7: Improvement of IBS-SSS and improvement of BMI



Scatterplot showing the improvement of IBS-SSS and the improvement of BMI during the conservative weight loss intervention described in paper 3. Each dot symbolizes a subject.

During the conservative weight loss intervention, improvement in IBS-SSS was negatively associated with improvement in BMI. As shown in figure 7, some of the subjects with the highest and most satisfying weight loss did have a

worsening in their bowel symptoms. The questions in IBS-SSS concern abdominal pain, abdominal distention, satisfaction with bowel habits and how much abdominal problems interfere with life in general. In paper 3, we did use FODMAPs to explain this inverse relation: It was probable that subjects with strict adherence to the recommendations had increased the proportion of FODMAPs in their diet, which could have led to abdominal symptoms. Another even simpler explanation could be that very low food intake led to constipation or hunger; two phenomena that also could have been captured on the IBS-SSS. The number of individual observations that made the association significant was low (two crosses bottom right and two top left in figure 7 did impact a lot on the total numbers) and the negative association might also have been coincidental. At least, we did not see any positive association between BMI loss and IBS-SSS improvement, and the theory that some inflammatory signal substance secreted from fat tissue is the leading cause of IBS in MO [55] was slightly weakened by our data.

The first submitted version of paper III led a reviewer to reply ʻThe authors seem to indicate that weight loss alone can be the cause of these findings.' It is true that by focusing on a conservative and not a surgical weight loss intervention, we aimed to reduce errors introduced by postoperative abdominal pain. We tried to clarify in the final version of the paper that a study of a conservative weight loss intervention is not a study of the effect of weight

loss itself. A conservative weight loss intervention in outpatient individuals leads to many different consequences in addition to the weight change.

Some small alterations in the logistics of dietary registration could have improved the data set. Diet registration at the second clinical control and diet registration from the subjects recruited at Aker would have increased the possibilities to detect important associations. We could also have focused more on mental distress in our collection and evaluation of the data. Several lines of evidence indicate that psychological factors play a significant role in IBS in MO.

Dysbiosis, as measured by the GA test, was not associated with IBS in MO in our cohort. However, the microbiota is much more than what is evaluated in a dichotomized classification of dysbiosis [115]. Recently, microbiota signatures associated with IBS severity [58] and microbiota profiles associated with response to the FODMAP diet [116, 117] have been identified. If such findings can be reproduced in several independent populations, the microbiome might soon become clinically relevant in IBS.

Systemic inflammation related to the amount of fat tissue did not seem to be the leading cause of IBS in MO. Many different inflammatory markers can be measured in the blood, and several cytokines are important in the pathophysiology of obesity and have been associated with IBS [51, 56]. In the three papers included in this thesis, we focused on CRP as the molecule has

attractive diagnostic properties and has been associated both with MO and IBS [7, 9]. The absence of associations between IBS and CRP does not exclude that local inflammation in the gut is very important in the aetiology of IBS in MO: Alterations of mast cells or lymphocytes locally in the gut would be expected to be independent of changes in the systemic CRP level [4, 118, 119].

The relation between diet and IBS in the MO-BiPS cohort may be related to the function of the microbiota and local gut inflammation [71, 115]. Unfortunately we were not able to measure local inflammation in the gut mucosa or the detailed composition and function of the microbiome in our research project [57]. Many exciting hypotheses related to interaction between diet, microbiome and inflammation have been presented and could be explored further in human studies [69]. The many possible analyses and endpoints in microbiome and inflammation research do however lead to a danger of storytelling bias. Honesty about whether hypotheses were made before the results were seen is important [62, 104, 120].

The results in paper I could also be used to speculate that IBS in MO also might be related to altered thyroid function or fatty liver disease [121, 122]. We know that thyroid hormones affect the gut motility [123]. It is not implausible that gut symptoms related to thyroid function can appear before a patient is diagnosed with hypothyroidism, or that extensive accumulation of fat in the liver might lead to bowel symptoms [122].

Whether IBS and MO as currently defined are the most meaningful disease categories is another intriguing discussion. As mentioned in several sections of this thesis, both IBS and MO could be considered as phenotypes that can be caused by many different and overlapping etiologies. It is notable that both IBS and MO are diagnosed by criteria that have been defined at consensus conferences. Identification of subgroups of IBS or MO that have much in common might be very useful to create progress. Such subgroups could have the same aetiology and respond to the same therapy, and some of them should perhaps be defined as new diagnoses or subdiagnoses. Dysbiosis tests might have a future to identify microbiota-related IBS, and to identify probable responders to therapies targeting the microbiota. IBS in MO might be dominated by other subdiagnoses where symptoms can be improved by dietary or psychosocial intervention. From the history of medicine we are well aware that definition, delineation, and understanding of a disease often precede discovery of treatment. IBS might in the future not be considered as a common disorder that is notoriously difficult to treat, but rather as a number of different disorders that should be treated in different ways.

New findings

Diagnostics

The GA-map IBS dysbiosis test was unsuitable as a diagnostic test of IBS. Our results did not imply that all microbiome based tests for IBS or all tests based on the GA technology should be abandoned but is a reminder that new tests should be re-examined in independent populations before introduction in clinical practice.

Prevalence

We showed a threefold difference in prevalence rates of IBS in two populations of subjects with MO referred for the same reason and selected with identical criteria. Differences in diet might explain parts of this difference.

Treatment

Our research identified conservative weight loss programs as a treatment that might hold promise for patients with concurrent IBS and MO. 71% of our included subjects with IBS and MO at inclusion had a clinically significant improvement of IBS-SSS during the intervention.

Clinical implications

Since IBS is very common in some groups of subjects with MO, attention to bowel symptoms is important in the care of subjects with obesity. A half-year long conservative weight loss program alleviated bowel symptoms in subjects with concurrent IBS and MO. This contrasts to the increase in abdominal pain and IBS observed after bariatric surgery [26, 27]. A conservative weight loss program might become a reasonable first treatment approach when we meet patients where IBS and MO coexist.

Conclusions

Unhealthy diets and mental distress could explain the high IBS prevalence seen in some groups of subjects with MO. A new test of the microbiome was not a suitable diagnostic test for IBS. Bowel symptoms were reduced by a conservative weight loss program. Changes in mental distress and diet were probable reasons for this improvement.

Research on bowel symptoms in subjects with obesity is vulnerable to various kinds of bias and confounders, and a firm general conclusion that IBS is a complication of MO could not be drawn from our work.

Future studies

Study the prevalence of IBS in subjects with MO

A population-based study where a large selection of a general population answer the Rome III criteria, can give us more answers about the association between IBS and MO. Such analyses could for instance be done in the Nord-Trøndelag health study. Epidemiological studies have advantages compared to studies in patients recruited from hospital outpatient clinics.

Evaluate a faecal test of microbial dysbiosis for the diagnosis of IBS

Further evaluation of the dysbiosis test could also be done in a sample of subjects from a general population instead of using patients with MO recruited at a hospital. A future study could include about 500 subjects randomly selected from the general population, where about 40-50 subjects would be expected to have IBS. The design should contain as much blinding as possible. Such a study could lead to a final conclusion about whether the dysbiosis test could have a future as a diagnostic test. The study could be combined with metagenomic sequencing or 16S rRNA sequencing to test the technical reliability of the dysbiosis test.

Hotel studies on obesity, diet and bowel symptoms

The conservative weight loss program in our study was performed as outpatient visits. If a part of this weight loss program had been done with the subject living in a hotel, eating all food from a buffet, we could have collected information at a higher precision level. Photography of plates before and after eating, repeated questionnaires, registration of all bowel movements, microbiome tests and repeated biopsies of the gut and fat tissue could have been organized. Such data collection combined with randomization of the subjects to different interventions could give us precise ideas about mechanisms, but such studies would be expensive to perform.

Study the impact of bariatric surgery on IBS

Paper III evaluated effects of a non-surgical intervention. A prospective study that evaluates subjects with the Rome III criteria before and with frequent time intervals after bariatric surgery would give clinically interesting information about what subjects with IBS and MO could expect after bariatric surgery. Randomization to conservative or surgical intervention would be research of high value but might be hard to organize in a period where bariatric surgery is very available.

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Errata

In Paper I, Table 1 the percentage of IBS at Innlandet Hospital Trust Gjøvik should have read *37/139 (27%)* and not *37/139 (26%)*.

Appendices

Appendix 1: Paper I

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RESEARCH ARTICLE Open Access

Prevalence and predictors of irritable bowel syndrome in patients with morbid obesity: a cross-sectional study

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Abstract

Background: Irritable bowel syndrome has been reported as more common in patients with morbid obesity than in the general population. The reason for this association is unknown. The aims of this study were to study the prevalence of irritable bowel syndrome and other functional bowel disorders in patients with morbid obesity, and to search for predictors of irritable bowel syndrome.

Methods: Patients opting for bariatric surgery at two obesity centers in South-Eastern Norway were included. Functional bowel disorders were diagnosed according to the Rome III criteria. Predictors were evaluated in a multivariable logistic regression analysis with irritable bowel syndrome as the dependent variable.

Results: A total of 350 (58%) out of 603 consecutive patients were included. The prevalence rates of irritable bowel syndrome at the two centers were 17/211 (8%) and 37/139 (27%) respectively. High low-density lipoprotein (OR 2.10; 95% CI 1.34–3.29), self-reported psychiatric disorders (OR 2.39; 95% CI 1.12–5.08) and center (OR 5.22; 95% CI 2.48–10.99) were independent predictors of irritable bowel syndrome.

Conclusions: At one of the two obesity centers, the prevalence of irritable bowel syndrome was threefold higher than in the general population in the same region. The high prevalence appears to be related to dietary differences or altered absorption or metabolism of fat. Attention to irritable bowel syndrome is important in the care of patients with morbid obesity.

Keywords: Irritable bowel syndrome, Functional bowel disorders, Morbid obesity, Abdominal pain, Functional gastrointestinal disorders, Low-density lipoprotein

Background

Irritable bowel syndrome (IBS) has a prevalence of about 7% in North America and Europe [1]. Abdominal pain or discomfort is the main symptom [2]. The pathophysiology includes disturbances of the gut-brain axis, low-grade mucosal immune activation and changes in the fecal microbiota [3, 4]. Because no biomarker is available, the gold standard for the diagnosis is symptom-based criteria [2, 5, 6]. IBS is more prevalent in women than in men and is associated with several comorbid conditions including anxiety and depression [7].

Most reports indicate that IBS is more common in patients with morbid obesity than in the general population, with prevalence rates from 8 to 31% in small series [8–12]. The reason for this association is unknown [13]. Pathophysiological factors that are common for IBS and MO, including psychological distress, low-grade systemic inflammation and vitamin deficiencies, could explain the association [3, 14–19]. Insights into the risk factors of IBS among patients with morbid obesity might help to prevent this burdensome condition in patients with obesity, and improve our knowledge of the general pathophysiology of IBS.

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The aims of this study were to explore the prevalence of IBS, subtypes of IBS and other functional bowel disorders and to search for predictors of IBS in two groups of patients with morbid obesity.

Methods

Study design and setting

In this cross-sectional study, adult patients referred to two obesity centers providing bariatric surgery in South-Eastern Norway were invited to participate. Oslo University Hospital Aker (OUH-A) recruited patients living in an urban area and Innlandet Hospital Trust Gjøvik (IHT-G) recruited patients living in rural areas and small towns. The medical history, current medications and anthropometric evaluations including BMI were registered on the day of inclusion. A routine clinical examination was performed and blood samples were retrieved. Demographics and comorbidity were reported by the patients in a paper-based case report form. All patients filled in questionnaires for the classification of functional bowel disorders. Additional diagnostic procedures including endoscopic examinations were done at the discretion of the attending physician. Patients at OUH-A and IHT-G were recruited from February 2014 through April 2015, and from December 2012 through September 2014, respectively.

Participants

The inclusion criteria were age 18–65 years and morbid obesity, defined as BMI > 40 kg/m^2 or BMI >35 kg/m^2 with obesity-related comorbidity at the time of referral [20]. Exclusion criteria were major psychiatric disorders (schizophrenia, major depression or bipolar disorder), alcohol and drug addiction, organic gastrointestinal disorders, former obesity surgery and other major abdominal surgery. The case report form was printed in Norwegian, and patients not able to understand Norwegian were excluded. At IHT-G, patients were included only 3 days per week when the study nurse was present.

Variables

Demographics

Seven demographic variables were registered: Age (years), sex (male/female), ethnicity (% Caucasian), BMI (kg/m^2), smoking habits (smoking/not smoking), work status (full-time/part-time/not working) and cohabitant status (living with partner/not living with partner).

Comorbidity and use of medication

Six present or previous comorbidities were reported by the patient on the case report form: Diabetes mellitus, hypothyroidism, hypertension, fibromyalgia, gallstones and self-reported psychiatric disorders. At OUH-A, the subjects were asked if they had been diagnosed with anxiety or depression (present/absent), and at IHT-G if they had sought professional help for psychiatric disorders (present/absent). At both centres, subjects with a diagnosis of major psychiatric disorders (schizophrenia, major depression or bipolar disorder) were excluded. When in doubt, the subjects were referred for a psychiatric evaluation. Regular use of medication was reported by the patients. All information concerning comorbidity and medication were reviewed by a clinician with full access to the patient's medical record.

Abdominal complaints

Functional bowel disorders were diagnosed with a validated Norwegian translation of the Rome III questionnaire [2]. IBS and subtypes of IBS, functional constipation, functional diarrhea and functional bloating were coded as present/absent.

Blood tests

Thirty-tree variables were analyzed from the blood samples. The reference values for the 15 variables reported in the results were as follows: hemoglobin g/dl: women 11.7–15.3, men 13.4–17.0; white-cell count 10^9/l: 3.5–10.0; platelet count 10^9/l: 145–390; c-reactive protein (CRP) mg/l: <5; cholesterol mmol/l: age 18–29 2.9–6.1, age 30–49 3.3–6.9, age > 50 3.9–7.8; high-density lipoprotein mmol/l: women 1.0–2.7, men 0.8–2.1; low-density lipoprotein (LDL) mmol/l: age 18–29 1.3–4.3, age 30–49 1.5–4.8, age > 50 2.0–5.4; thyroid stimulating hormone (TSH) mIE/l: 0.27–4.20; free thyroxin (T_4) pmol/l: 8.0–22.0; vitamin B_1 nmol/l: 95–200; vitamin B_6 nmol/l: 15–160; vitamin B_{12} pmol/l: 140–650; folic acid nmol/l: 7–40; HbA_1C %: 4.0–6.0; total bilirubin μmol/l: 5–25. The other 18 variables were mean corpuscular volume, mean corpuscular hemoglobin, iron, transferrin, transferrin saturation, ferritin, transferrin iron binding capacity, sodium, potassium, magnesium, phosphate, glucose, creatinine, uric acid, alanine aminotransferase, total protein, albumin, and triglycerides.

Dietary registration

At IHT-G, the intake of micro- and macronutrients was estimated with a semi-quantitative food frequency questionnaire designed and validated for the Norwegian population [21].

Statistical analysis

Data are presented as mean (standard deviation), median (range) and proportion (percentage) according to the distribution of data. Student's t-test, Mann-Whitney U test, Pearson chi-squared test, or Fisher's exact test was used for the comparisons between the groups depending on the type of data and normality. Correlations were assessed with the Pearson or Spearman correlation

coefficients. Because the prevalence of IBS differed between the centers, the predictors of IBS were analyzed one-by-one with logistic regression adjusted for the center after testing for statistical interaction. The effect of TSH differed strongly from linear. Therefore, fractional polynomials were used to transform this variable. Predictors that were significant in these analyses were included as independent variables in a multivariable logistic regression analysis with IBS as the dependent variable. The results are presented as odds ratios with 95% confidence intervals (CI). The presented predictors of IBS include all predictors that were significant in the analysis corrected for center only and a selection of other relevant variables. In the posthoc analysis, we examined the differences between the groups of patients with and without IBS separately at the two centers. Two-sided p-values <0.05 were judged to indicate statistical significance. Data analysis was performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp) and Stata Statistical Software, Release 13 (College Station, TX: StataCorp LP).

Power calculation

The prevalence of IBS was 8.4% in the general population from the same area [14] and was expected to be 18% in patients with morbid obesity [9]. A study including 350 participants with morbid obesity was calculated to have a power of 98% to detect a difference between the general population and the patients with morbid obesity, with $\alpha = 0.01$.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway, references 2012/966 and 2013/1264, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Results

A total of 350 (58%) out of 603 consecutive patients eligible for study participation were included (Fig. 1). The prevalence rates of IBS were 17/211 (8%) at OUH-A and 37/139 (27%) at IHT-G ($p < 0.001$), and the prevalence rates of functional constipation were 20/205 (10%) and 3/135 (2%) respectively ($p = 0.006$). Table 1 gives patients' characteristics at the two centers with comparisons between the groups.

High serum levels of LDL, self-reported psychiatric disorders and center were independent predictors of IBS

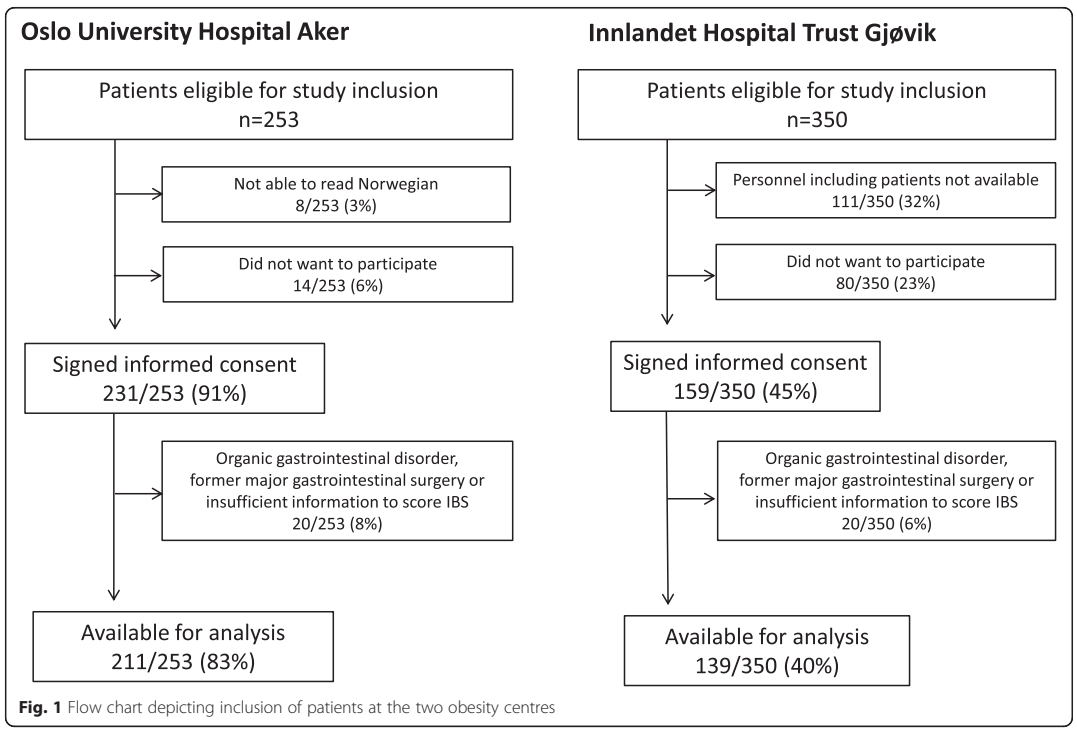

Fig. 1 Flow chart depicting inclusion of patients at the two obesity centres

Table 1 Patients' characteristics at the two centers

	Oslo University Hospital Aker		Innlandet Hospital Trust Gjøvik		
		n		n	*p*-value
Gender (%male)	62 (29%)	211	28 (20%)	139	0.05#
Age (years)	43 (21–61)	211	44 (24–61)	139	0.66*
Body mass index (kg/m^2)	43 (33–62)	211	42 (35–53)	139	0.09*
Ethnicity (% Caucasian)	195 (93%)	210	139 (100%)	139	0.001#
Irritable bowel syndrome (IBS)	17/211 (8%)	211	37/139 (26%)	139	<0.001#
IBS-constipation	3/17 (18%)	17	7/37 (19%)	37	0.48#
IBS-diarrhea	2/17 (12%)	17	11/37 (30%)	37	
IBS-mixed	11/17 (65%)	17	18/37 (49%)	37	
IBS-unsubtyped	1/17 (6%)	17	1/37 (3%)	37	
Functional bloating	21/205 (10%)	205	19/138 (14%)	138	0.32#
Functional constipation	20/205 (10%)	205	3/135 (2%)	138	0.006#
Functional diarrhea	9/206 (4%)	206	4/139 (3%)	139	0.48#
Smoking	56/204 (28%)	204	24/139 (17%)	139	0.03#
Diabetes mellitus	53/211 (25%)	211	26/139 (19%)	139	0.16#
Hypothyroidism	19/211 (9%)	211	17/138 (12%)	138	0.32#
Fibromyalgia	20/211 (10%)	211	25/138 (18%)	138	0.02#
Self-reported psychiatric disorder	36/211 (17%)	211	29/139 (21%)	139	0.37#
Hemoglobin (g/dl)	14.1 (1.1)	211	14.5 (1.1)	136	0.006
White-cell count (×10^9/l)	7.4 (2.4–13.3)	210	7.5 (4.2–16.1)	136	0.95*
Platelet count (×10^9/l)	275 (112–519)	210	276 (131–939)	134	0.46*
HbA_1C (%)	5.8 (4.7–14.9)	211	5.5 (4.5–11.5)	136	<0.001*
Bilirubin (μmol/l)	7 (2–23)	210	6 (2–28)	136	0.07*
C-reactive protein (mg/l)	7 (1–50)	210	5 (0–43)	136	0.01*
Cholesterol (mmol/l)	4.9 (1.0)	210	5.1 (1.0)	136	0.10
High-density lipoprotein (mmol/l)	1.1 (0.5–2.0)	210	1.1 (0.4–2.2)	136	0.70*
Low-density lipoprotein (mmol/l)	3.1 (0.9)	210	3.3 (0.9)	136	0.02
Thyroid stimulating hormone (mIE/l)	1.4 (0–14.6)	210	1.7 (0–6.9)	136	0.11*
Free T_4 (pmol/l)	15 (11–28)	210	15 (10–26)	136	0.30*
Vitamin B_1 (nmol/l)	156 (62–239)	210	153 (104–246)	135	0.70*
Vitamin B_6 (nmol/l)	29 (5–231)	211	22 (5–209)	133	0.01*
Vitamin B_{12} (pmol/l)	344 (158–1480)	211	346 (158–1401)	136	0.80*
Folic acid (nmol/l)	18 (6–46)	211	17 (7–46)	136	0.14*
Use of statins	35/211 (17%)	211	19/138 (14%)	138	0.48#
Use of thyroid substitution therapy	19/211 (9%)	211	13/139 (9%)	139	0.91#

The results are given as number (proportion in percent) for categorical variables, mean (standard deviation) for continuous variables with normal distribution and median (range) for other continuous variables. Data were analyzed with with t-tests, Pearson chi-squared tests (marked with #) or Mann-Whitney U test (marked with *)

(Table 2). Table 3 gives the comparisons between patients with and without IBS at each center, and comparisons between patients with IBS at the two centers. TSH was higher, and free T_4 was lower among the IBS patients at IHT-G compared to those at OUH-A. LDL levels in the blood correlated with higher relative energy intake from saturated fat (r = 0.26, p = 0.01) and mono-unsaturated fat (r = 0.25, p = 0.01). Patients with IBS had lower relative energy intake from proteins. No other significant differences in nutrition between patients with and without IBS were observed (Table 4).

Discussion

The prevalence of IBS in patients with morbid obesity varied significantly between the two centers. At OUH-A, the prevalence (8%) was comparable with that in the

Table 2 Predictors of irritable bowel syndrome (IBS)

			Adjusted for center only		Adjusted for all significant predictors	
	Patients without IBS	Patients with IBS	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Gender (%male)	84 (28%)	6 (11%)	0.35 (0.14–0.87)	0.02	0.57 (0.18–1.82)	0.34
Age (years)	44 (21–61)	41 (23–61)	0.97 (0.94–1.00)	0.07		
Body mass index (kg/m^2)	42 (33–62)	42 (36–53)	0.98 (0.92–1.06)	0.64		
Ethnicity (% Caucasian)	281/296 (95%)	53/54 (98%)	1.34 (0.17–10.82)	0.51		
Smoking	68/291 (23%)	12/52 (23%)	1.24 (0.60–2.59)	0.56		
Diabetes mellitus	72/296 (24%)	7/54 (13%)	0.51 (0.22–1.20)	0.12		
Hypothyroidism	29/296 (10%)	7/53 (13%)	1.27 (0.51–3.16)	0.61		
Fibromyalgia	33/295 (11%)	12/54 (22%)	1.86 (0.86–4.00)	0.12		
Self-reported psychiatric disorder	47/296 (16%)	18/54 (33%)	2.61 (1.33–5.13)	0.005	2.39 (1.12–5.08)	0.02
Hemoglobin (g/dl)	14.3 (1.1)	14.0 (1.1)	0.65 (0.49–0.88)	0.004	0.68 (0.45–1.02)	0.07
White-cell count (×10^9/l)	7.5 (2.8–16.1)	7.3 (2.4–11.3)	0.85 (0.72–1.00)	0.05		
Platelet count (×10^9/l)	275 (112–519)	294 (131–939)	1.00 (1.00–1.01)	0.14		
C-reactive protein (mg/l)	6 (0–50)	5 (1–23)	0.97 (0.92–1.03)	0.33		
Cholesterol (mmol/l)	4.9 (1.0)	5.4 (0.8)	1.73 (1.23–2.43)	0.002		
High-density lipoprotein (mmol/l)	1.1 (0.4–2.2)	1.1 (0.7–2.0)	1.02 (0.39–2.67)	0.97		
Low-density lipoprotein (mmol/l)	3.1 (0.9)	3.6 (0.7)	1.85 (1.27–2.70)	0.001	2.10 (1.34–3.29)	0.001
Thyroid stimulating hormone (mIE/l)	1.5 (0.0–7.9)	1.7 (0.2–14.6)		0.02		0.08
Free T_4 (pmol/l)	15 (10–28)	15 (11–23)	0.97 (0.85–1.10)	0.17		
Vitamin B_1 (nmol/l)	155 (62–239)	142 (91–246)	0.98 (0.97–1.00)	0.008	0.99 (0.98–1.01)	0.21
Vitamin B_6 (nmol/l)	26 (5–231)	26 (6–113)	0.99 (0.98–1.01)	0.36		
Vitamin B_{12} (pmol/l)	346 (158–1480)	342 (173–712)	1.00 (1.00–1.00)	0.52		
Folic acid (nmol/l)	18 (6–46)	16 (7–46)	0.98 (0.94–1.02)	0.28		
Use of statins	52/295 (18%)	2/54 (4%)	0.18 (0.04–0.78)	0.02	0.31 (0.07–1.47)	0.14
Use of thyroid substitution therapy	26/296 (9%)	6/54 (11%)	1.30 (0.49–3.46)	0.60		
Center					5.22 (2.48–10.99)	<0.001

The results are given as number (proportion in percent) for categorical variables, mean (standard deviation) for continuous variables with normal distribution and median (range) for other continuous variables. In the column "Adjusted for center only", comparisons between patients with and without IBS were performed with logistic regression adjusted for center. In total, 48 potential predictors were examined. The 25 predictors presented in the tables are all predictors with significant associations with IBS and a selection of other potential predictors of clinical interest. In the column "Adjusted for all significant predictors", gender, self-reported psychiatric disorders, hemoglobin, low-density lipoprotein, thyroid stimulating hormone, vitamin B_1, use of statins and center were included in the final logistic regression analysis with 342 patients. Cholesterol is not included in the final analysis due to high correlation with LDL. No odds ratio for thyroid stimulating hormone is available as the variable is transformed with fractional polynomials

general population [1, 7]. At IHT-G, the prevalence (27%) was three-fold that in the general population from the same region [14]. A high prevalence of IBS is consistent with most other reports from obesity centres [8–10].

High serum LDL levels and self-reported psychiatric disorders were independent predictors of IBS. An association between LDL and IBS has been reported in some, but not all earlier studies [22, 23]. Dietary differences or altered fat absorption or metabolism are possible explanations for the association between IBS and high LDL.

Dietary differences can influence on IBS symptoms [24, 25]. High LDL levels can be considered as a biomarker of a diet rich in saturated fats and low in fibre [26]. A difference in diet is a probable reason for higher levels of LDL in the subjects with IBS. Dietary registrations on a subset of the patients give support to this hypothesis, with correlations between the intakes of saturated and monounsaturated fats and LDL. Subjects with and without IBS ingested comparable amounts of carbohydrates, fibre, grains and vegetables.

Altered fat absorption in patients with IBS, possibly associated with local low-grade inflammation in the gut or alteration of the gut microbiome [3, 27] could also explain raised LDL levels. Altered fat metabolism is a third explanation. Blood lipoprotein levels are mainly regulated by the hepatocytes. Non-alcoholic fatty liver disease, which could influence the function of hepatocytes, is strongly related to obesity and has been discussed in relation to IBS [8, 28, 29]. Data on fatty liver disease were not available.

Table 3 Comparisons between patients with and without irritable bowel syndrome (IBS) at the two centers

	Oslo University Hospital Aker			Innlandet Hospital Trust Gjøvik			
	No IBS $n = 194$	IBS $n = 17$	p-value	No IBS $n = 102$	IBS $n = 37$	p-value	Differences between patients with IBS at the two centers (p-values)
Fibromyalgia	19/194 (10%)	1/17 (6%)	0.71[##]	14/101 (14%)	11/37 (30%)	0.03[#]	0.08[##]
Self-reported psychiatric disorder	30/194 (16%)	6/17 (35%)	0.04[#]	17/102 (17%)	12/37 (32%)	0.04[#]	0.84[#]
Hemoglobin (g/dl)	14.2 (1.1)	13.8 (1.1)	0.23	14.6 (1.0)	14.0 (1.1)	0.006	0.53
HbA_1C (%)	5.8 (4.7–14.9)	5.5 (4.9–7.3)	0.02*	5.4 (4.5–11.5)	5.5 (4.9–9.7)	0.52*	0.94*
Bilirubin (μmol/l)	7 (2–23)	7 (4–19)	0.94*	7 (2–28)	5 (2–15)	0.03*	0.07*
Cholesterol (mmol/l)	4.9 (1.0)	5.1 (0.8)	0.44	4.9 (1.0)	5.5 (0.8)	0.001	0.05
Low-density lipoprotein (mmol/l)	3.1 (0.9)	3.3 (0.7)	0.26	3.2 (0.9)	3.7 (0.7)	0.001	0.07
Thyroid stimulating hormone (mU/l)	1.5 (0.0–7.9)	1.4 (0.2–14.6)	0.31*	1.5 (0.0–5.5)	2.1 (0.8–6.9)	0.001*	0.007*
Free T_4 (pmol/l)	15 (11–28)	16 (12–23)	0.14*	16 (10–26)	15 (11–21)	0.04*	0.02*
Vitamin B_1 (nmol/l)	157 (62–239)	145 (91–176)	0.03*	155 (104–232)	142 (112–246)	0.04*	0.58*
Use of statins	34/194 (18%)	1/17 (6%)	0.32[##]	18/101 (18%)	1/37 (3%)	0.02[#]	0.54[##]

The results are given as number (proportion in percent) for categorical variables, mean (SD) for continuous variables with normal distribution and median (range) for other continuous variables. All the predictors that showed significant associations with IBS ($p < 0.05$) at one of the two centers are shown in the table. The differences between patients with and without IBS at Oslo University Hospital Aker, between patients with and without IBS at Innlandet Hospital Trust Gjøvik and between patients with IBS at Innlandet Hospital Trust Gjøvik and patients with IBS at Oslo University Hospital Aker are analyzed with t-tests, Pearson chi-squared tests (marked with [#]), Mann-Whitney U test (marked with *) or Fisher's exact test (marked with [##])

The association between IBS and self-reported psychiatric disorders is in accordance with studies in patients with morbid obesity and in the general population [7, 8, 14], patients with morbid obesity are known to have higher levels of stress, anxiety, and depression [15]. Associations between IBS and vitamin B_6 deficiency [18, 19] and low-grade systemic inflammation measured as CRP [16, 17] were not seen in this study.

The difference in the prevalence rates of IBS at the two centres rendered post hoc examinations desirable. Hemoglobin, bilirubin, cholesterol, LDL, TSH and free T4 all showed statistically significant differences between patients with and without IBS at IHT-G, but not at OUH-A. In addition, the comparisons of patients with IBS at the two centres also revealed differences in the thyroid function (Table 3). It is unlikely that accidental

Table 4 Diet in patients with and without irritable bowel syndrome (IBS)

Macronutrient or food group	No IBS $n = 70$	IBS $n = 27$	p-value
Carbohydrate (% of total energy intake)	43 (6)	45 (10)	0.20
Sugar (% of total energy intake)	5 (1–14)	5 (1–56)	0.34[#]
Protein (% of total energy intake)	19 (3)	17 (4)	0.04
Fat (% of total energy intake)	35 (6)	35 (9)	0.94
Saturated fat (% of total energy intake)	12 (2)	13 (4)	0.46
Monounsaturated fat (% of total energy intake)	12 (3)	12 (3)	0.95
Polyunsaturated fat (% of total energy intake)	7 (2)	6 (2)	0.52
Dietary fiber intake (intake in g/day)	33 (11)	32 (9)	0.53
Bread (intake in g/day)	176 (74)	175 (80)	0.99
Other cereals (intake in g/day)	54 (42)	70 (62)	0.14
Cakes (intake in g/day)	27 (44)	22 (24)	0.59
Potatoes (intake in g/day)	67 (48)	67 (51)	0.94
Vegetables (intake in g/day)	345 (197)	301 (166)	0.31
Fruit and berries (intake in g/day)	320 (251)	295 (188)	0.64

The results are given as mean (SD) for continuous variables with normal distribution and median (range) for other continuous variables. Energy intake and intake of different food groups are estimated from food frequency questionnaires in a subset of 97 patients recruited at Innlandet Hospital Trust Gjøvik. Differences between patients with and without IBS are analyzed with t-tests and Mann-Whitney U test (marked with [#])

circumstances or small sample sizes explain these findings. Minor differences in the analyses at the local laboratories could in part explain the differences between the patients at the two centres (Table 1), but not the differences between patients with and without IBS at each centre. It, therefore, seems to be true differences between the patients at the two hospitals, in particular among the patients with IBS. OUH-A had a long tradition for bariatric surgery and recruited patients from an urban region, whereas IHT-G was a new center for bariatric surgery in a rural region. The patients at a new centre for bariatric surgery will probably differ from patients seen at a centre with long traditions. Different health care and screening of the patients in the urban region may influence the presence of comorbidity and lifestyle (e.g. IBS, thyroid dysfunction, unhealthy diet) when evaluated at the center. Dietary differences with an unhealthy fatty diet in the rural area might have contributed to the differences in lipid values and IBS. Hypothyroidism can lead to gastrointestinal symptoms including abdominal pain [30], and thyroid dysfunction might have contributed to the high prevalence of IBS at IHT-G. This study indicated that changes in the lipid metabolism and thyroid dysfunction might be poorly recognized causes of IBS in general and in patients with morbid obesity in particular. These findings could in part explain the differences between the study centres. Differences in prevalence rates of functional gastrointestinal disorders in patients recruited from different types of secondary clinics (gastroenterological or obesity clinics) have recently been highlighted by Bouchoucha et al. [11] The current study shows that large differences also exist between clinics of the same type (two obesity clinics).

Abdominal pain is common after bariatric surgery [31], and the clinical evaluation usually focuses on surgical complications. The current research on IBS in patients with morbid obesity indicate that IBS is an important cause of abdominal pain before bariatric surgery, and probably remains so after surgery [32, 33]. Risk factors of IBS identified before surgery may also be important after surgery.

This study is in agreement with other studies showing widely different prevalence rates of gastrointestinal comorbidities among patients referred to different obesity centres [8–12]. The observations indicate that the diet could be a modifiable risk factor of IBS in this group of patients. The high prevalence of IBS is relevant for the clinical care of patients with morbid obesity, and the differences in the prevalence rates between centres before surgery are of importance for the evaluation of abdominal pain and discomfort in different cohorts after bariatric surgery.

Strengths and limitations

Both centres used a validated Norwegian translation of the Rome III questionnaire in similar clinical settings. The study population was judged as representative for the subjects referred to the clinics during the study period. The presence of the study nurse only 3 days per week at IHT-G did not reduce the representativeness.

The difference in the prevalence rates and the different size of the study population at the two centres exclude a valid and generalised conclusion about the prevalence of IBS in subjects referred for bariatric surgery. A possible contributing explanation for the high prevalence rate of IBS at IHT-G could be that before filling in the Rome III questionnaire, the subjects were asked about food intolerance and food related abdominal symptoms, which could have induced a recall bias and report of more abdominal discomfort.

The comprehensive evaluation of the patients strengthened the possibility to detect predictors of IBS and differences between the centres, but also increased the risk of type I errors. Other and more precise predictors could have strengthened the study further. Dietary registrations were done only in a subset of the subjects patients and did not contain information about fermentable oligosacchardies, disaccharides, monosacchardies and polyols (FODMAPs), and inflammation markers were restricted to CRP. Also, a more precise diagnosis of the psychiatric disorders had been desirable. The blood tests were analysed at the local laboratories which limited comparisons between the centres, but did not affect the comparisons between patients with and without IBS at each centre and was adjusted for in the multivariate analyses (Table 2).

Conclusions

The prevalence of IBS varied threefold between the two study centres. High LDL in serum and self-reported psychiatric disorders were predictors of IBS. Thyroid dysfunction might have contributed to the observed differences between the centres. A high intake of saturated fat and thyroid dysfunction could be modifiable risk factors of IBS, and attention to IBS is important in the care of patients with morbid obesity.

Abbreviations

BMI: Body mass index; CI: Confidence interval; CRP: C-reactive protein; IBS: Irritable bowel syndrome;; IHT-G: Innlandet Hospital Trust Gjøvik; LDL: Low-density lipoprotein; OUH-A: Oslo university hospital Aker; T_4: Free thyroxin; TSH: Thyroid stimulating hormone

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Availability of data and materials

Case report forms on paper were used for collection of the clinical data and are all safely stored. The data were transferred manually to SPSS for statistical analyses. The data files are stored by Innlandet Hospital Trust, Brumunddal, Norway, on a server with security according to the rules given by The

Norwegian Data Protection Authority, P.O. Box 8177 Dep. NO-0034 Oslo, Norway. The data are available on request to the corresponding author.

Authors' contributions
PGF is the guarantor of the project. He designed the study and analyzed data in collaboration with MA and SL. MA has recruited patients at Innlandet Hospital Trust, analyzed data and prepared the manuscript. IH, JK, TM and IE organized the project and recruited patients at Oslo University Hospital and participated in planning of the study concept. All authors have participated in the writing and have approved the last version.

Authors' information
Not applicable.

Ethics approval and consent to participate
The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics, PB 1130, Blindern, 0318 Oslo, Norway (reference numbers 2012/966 and 2013/1264) and performed in accordance with the Declaration of Helsinki. Written informed consent was given by all participants before inclusion.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Appendix 2: Paper II

Appendix 3: Paper III

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Research Article

A Conservative Weight Loss Intervention Relieves Bowel Symptoms in Morbidly Obese Subjects with Irritable Bowel Syndrome: A Prospective Cohort Study

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Background. Irritable bowel syndrome (IBS) is common in subjects with morbid obesity; the effect of weight loss programs on bowel symptoms is largely unknown. *Methods*. This prospective cohort study explored bowel symptoms, health scores, and biomarkers in subjects with morbid obesity during a six-month-long conservative weight loss intervention. Bowel symptoms were assessed with IBS-severity scoring system (IBS-SSS) and Gastrointestinal Symptom Rating Scale-IBS. Changes in all variables and associations between the changes in bowel symptoms and the other variables were analysed. *Results*. Eighty-eight subjects (81% females) were included. Body mass index was reduced from 42.0 (3.6) to 38.7 (3.5) ($p < 0.001$). IBS-SSS was reduced from 116 (104) to 81 (84) ($p = 0.001$). In all, 19 out of 25 variables improved significantly. In subjects with and without IBS at inclusion, the improvement in IBS-SSS was 88 (95% CI 55 to 121) and 10 (95% CI −9 to 29), respectively. Improved bowel symptoms were associated with improved subjective well-being, sense of humour, and vitamin D and negatively associated with reduced body mass index. *Conclusion*. Body mass index and health scores improved during a conservative weight loss intervention. Subjects with IBS before the intervention had a clinically significant improvement in bowel symptoms.

1. Introduction

Several gastrointestinal disorders have been associated with high body mass index (BMI) in population-based studies, and both upper gastrointestinal disorders and bowel disorders are considered as complications of obesity [1–3]. Knowledge about the effect of weight loss programs on functional bowel disorders is limited [4, 5]. Irritable bowel syndrome (IBS) is a functional bowel disorder that is present in about 11% of the global population and even more common in some groups of patients with morbid obesity (MO) [6, 7]. The main symptom of IBS is recurrent abdominal pain or discomfort related to defecation [8]. IBS has a high impact on quality of life and ability to work and is associated with many comorbidities, including pain syndromes and psychiatric disorders [9].

The aetiology of IBS is an interplay between central psychological factors and peripheral intestinal factors. Some pathophysiological factors have been reported both in patients with IBS and in patients with MO: psychological distress, dietary factors, an altered gut microbiome, and low-grade inflammation [9–17]. Associations between the cytokines secreted by adipose tissue and some of the comorbidities of obesity are plausible, and systemic low-grade inflammation might be a cause of IBS in subjects with MO [18].

Dietary interventions are parts of the treatment of both IBS and MO. A reduced intake of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) will often relieve IBS symptoms, and a variety of low-energy diets can lead to weight reduction in subjects with obesity [19, 20].

The primary aim of this study was to compare bowel symptoms and IBS before and after a conservative weight loss intervention. Secondary aims were to study changes in several health scores and biomarkers during the intervention and to explore the associations between the changes in the bowel symptoms and the other variables.

2. Materials and Methods

2.1. Study Design and Setting. Adults referred to an outpatient obesity clinic in South Eastern Norway from December 2012 to September 2014 were invited to participate in this prospective cohort study. Information was collected at the visits before and after a six-month-long weight loss intervention period. The visits included anthropometric evaluations and retrieval of blood samples. The subjects reported symptoms, demographics, and comorbidity on a paper-based case report form. A physical examination was performed. Additional diagnostic procedures including endoscopic examinations were done at the discretion of the attending physician.

2.2. Participants. The inclusion criteria were age 18–65 years and morbid obesity, defined as either BMI > 40 kg/m^2 or BMI > 35 kg/m^2 with complications (diabetes mellitus, hypertension, sleep apnoea, respiratory failure, or musculoskeletal pain related to movement) [21]. Exclusion criteria were organic gastrointestinal disorders; major psychiatric disorders; serious somatic disorders not related to obesity, alcohol, or drug addiction; previous obesity surgery; and other major abdominal surgery. Subjects with insufficient information to assess IBS were also excluded. The inclusion of subjects is depicted in Figure 1.

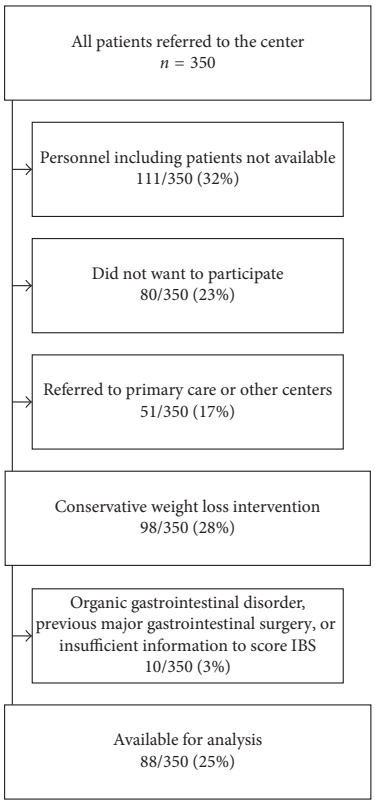

Figure 1: Inclusion of subjects.

2.3. Intervention. The weight loss intervention lasted for approximately six months. First, the subjects had three separate one-hour-long individual consultations with a nurse, a dietician, and a physician who gave advice on lifestyle and diet. The advice was personalised based on the subjects' exercise habits and preferences, food preferences, and former diet. The time intervals between the appointments were individualised to give the subjects time to implement the changes. In the middle of the six-month intervention period, the subjects were enrolled in groups of eighteen to twenty who had weekly four-hour meetings for seven consecutive weeks. These meetings consisted of group counselling, a lunch together, and lectures by dieticians, physicians, nurses, and a psychologist about awareness and habits.

The lifestyle advice was focused on an increase in enjoyable physical activity, usually hiking in nature together with friends, biking, swimming, or cross-country skiing. The dietary advice was based on the reduction of total energy intake, use of less energy dense food, more fiber and protein, less sugar and fat, and more food rich in micronutrients. The subjects were recommended 4–6 meals per day with 2–4 hour intervals between meals. The last three weeks consisted of a strict "crisp bread diet" with an energy intake of 3765 kJ/day. In this period, the daily food intake was 4.5 dl of low-fat milk, 144 grams of rye-based crisp bread with low-fat, high-protein topping (low-fat cheese, meat, or fish), a small dinner dish (meat or fish), and free amounts of water, beverages without calories, and vegetables (all vegetables were accepted except sweet corn, olives, and avocados). The subjects were allowed to replace the crisp bread diet with meal replacement powder as long as the maximum energy intake remained below 3765 kJ/day. They were informed that acceptance to the public, free-of-charge bariatric surgery program partly depended on adherence to the conservative weight loss program [22].

2.4. Variables

2.4.1. Anthropometrics. Height and weight were registered to calculate BMI (kg/m^2).

2.4.2. Demographics. Five demographic variables were registered: age (years), gender (male/female), smoking habits (daily smoking/not daily smoking), employed (working/not working), and cohabitant status (living with partner/not living with partner).

2.4.3. Diseases. Nine present or previous diseases were registered (yes/no): hypertension, diabetes mellitus, myocardial infarction, stroke, fibromyalgia, psychiatric disorders, allergic rhinitis, chronic obstructive pulmonary disorder, and hypothyroidism.

2.4.4. Health Scores. Thirteen health scores were assessed:

(1) *Irritable bowel syndrome-severity scoring system (IBS-SSS)*: this has been developed for the use in clinical and research settings. The score ranges from 0 to 500. Mild, moderate, and severe degrees of IBS have been defined by scores of 75 to 175, 175 to 300, and >300, respectively. Subjects with IBS and a score below 75 are considered to be in remission, and a change of 50 has been judged as clinically significant [23, 24].

(2) *Gastrointestinal Symptom Rating Scale modified for use in patients with IBS (GSRS-IBS)*: this scale is an IBS-specific version of the Gastrointestinal Symptom Rating Scale. The score ranges from 1 to 7; high values indicate more discomfort. GSRS-IBS has five subscales: pain, bloating, constipation, diarrhoea, and satiety. The response scale is as follows: (1) no discomfort at all; (2) minor discomfort; (3) mild discomfort; (4) moderate discomfort; (5) moderately severe discomfort; (6) severe discomfort; and (7) very severe discomfort [25].

(3) *Rome III criteria*: these criteria were used to diagnose functional bowel disorders [8]. IBS and the IBS subtypes, functional bloating, functional constipation, and functional diarrhoea were noted as present or absent.

(4) *Hopkins Symptom Checklist (HSCL-10)*: this is a ten-item questionnaire that measures psychological distress/mental health. The score ranges from 1 to 4. High levels indicate high levels of psychological distress; 1.85 is a cutoff point for normality [26].

(5) *WHO-5 Well-Being Index (WHO-5)*: this is a five-item questionnaire that measures subjective well-being. It is a reliable measure of emotional functioning and a screening tool for depression. The index ranges from 0 to 100; high scores indicate better well-being. A score of 50 or below indicates low mood and a score of 28 or less indicates likely depression [27].

(6) *Rosenberg's Self-Esteem Scale*: this is a ten-item questionnaire that measures general self-esteem. The scale ranges from 0 to 30; high scores indicate a high self-esteem [28].

(7) *Fatigue Severity Scale (FSS)*: this is a nine-item questionnaire that measures fatigue (a sense of physical tiredness and lack of energy, distinct from sadness or weakness). The scale ranges from 1 to 7; high scores indicate a high level of fatigue. A threshold of 5 has been used to define high fatigue [29].

(8) *Epworth Sleepiness Scale*: this scale is an eight-item questionnaire that measures general daytime sleepiness. The scale ranges from 0 to 24; high scores indicate higher sleepiness [30].

(9) *Sense of Humour Questionnaire (SHQ-6)*: this is a six-item questionnaire that measures the sense of humour. The score ranges from 1 to 4; high scores indicate high sense of humour [31].

(10) *Suter's Questionnaire*: this is a questionnaire that measures food tolerance. The food tolerance score ranges from 1 to 27; high scores indicate good food tolerance [32].

(11) *Number of meals*: this was assessed with Suter's Questionnaire; both main meals and smaller meals were included in the count [32].

(12) *Musculoskeletal pain score*: this is a six-item questionnaire that measures the degree of musculoskeletal pain. It ranges from 0 to 12; high scores indicate more pain.

(13) *Physical activity score*: this is a two-item questionnaire. The first question asks about easy activity (not sweaty/breathless), and the second question asks about strenuous activity (sweaty/breathless). There are four alternatives to each question: none, under 1 hour, 1-2 hours, or 3 hours and more per week. For light activity, the four alternatives were scored as 0, 1, 2, and 3, respectively. For strenuous activity, the four answers were scored as 0, 3, 4, and 5, respectively. A score ranging from 0 to 8 was created by adding the scores for easy and strenuous physical activity, and a high score indicates high physical activity.

2.4.5. Blood Tests. Low-density lipoprotein, high-density lipoprotein, cholesterol, C-reactive protein (CRP), thyroid-stimulating hormone, thyroxin, HbA1c, vitamin B_{12}, vitamin B_1, vitamin B_6, and vitamin D were analysed.

2.4.6. Dietary Intake. In a subset of the patients, the intake of energy and some selected nutrients was registered at inclusion with a semiquantitative food frequency questionnaire designed and validated for the Norwegian population [33].

2.5. Statistical Analysis. Data have been presented as mean (standard deviation), median (range), and proportion (percentage) according to the type and distribution of data. The changes in the prevalence rates have been presented with a Newcombe 95% CI [34]. McNemar's test, Wilcoxon

signed-rank test, or paired t-test was used depending on the type of data and normality. The distributions of IBS categories before and after the intervention were compared with Stuart-Maxwell test for marginal homogeneity for nominal categories [34] and computed in Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX). Two-sided p values < 0.05 were judged to indicate statistical significance. When changes in a variable were significantly different in subjects with and without IBS (evaluated with Mann-Whitney U test), results were also presented stratified by IBS status.

Linear regression analyses were used for the study of the associations between improvements in IBS-SSS, GSRS-IBS, and BMI (dependent variables) and the improvement in one-by-one of the other variables (independent variables) with sex and age as covariates. Lower thyroid-stimulating hormone, higher thyroxine, and more meals/day were defined as improvements. The results of the linear regression analyses have been presented as B values with 95% confidence intervals, partial correlations (pc), and p values. To adjust for multiple testing, Benjamini-Hochberg false discovery rate adjusted q values were calculated in R [35]. Where not indicated, data analysis was performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY).

2.6. Ethical Approval. The study was approved by the Regional Committees for Medical and Health Research Ethics South East Norway, reference 2012/966, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the subjects included in the study.

3. Results

Eighty-eight subjects (71 (81%) females) with a mean age of 44 (SD 8) years were included (Table 1). The prevalence of IBS was 24/88 (27.3%) before and 17/88 (19.3%) after the intervention (Table 2). The change in prevalence was 8.0% (95% CI −18.2% to 2.4%, $p = 0.126$). GSRS-IBS showed a reduction in overall symptoms, bloating, diarrhoea, and satiety and an increase in constipation (Table 3). The distribution of IBS subtypes before and after the intervention did not differ significantly ($p = 0.36$). In subjects with and without IBS at the first visit, the improvement in IBS-SSS was 88 (95% CI 55 to 121) and 10 (95% CI −9 to 29), respectively (Table 4).

BMI was reduced from 42.0 (SD 3.6) to 38.7 (SD 3.5) kg/m^2. The change in BMI was 3.3 kg/m^2 (95% CI 3.0 kg/m^2 to 3.6 kg/m^2, $p < 0.001$). Psychological distress, subjective well-being, self-esteem, fatigue, sleepiness, and musculoskeletal pain improved. In blood, CRP, cholesterol, and low-density lipoprotein decreased and the levels of vitamin B_6, B_{12}, and D increased (Table 3). The recommended energy intake at the end of the intervention was less than half of the self-reported energy intake before the intervention, while the intake of bread and milk largely was unchanged (Table 5).

Table 1: Characteristics of the included subjects.

	Mean (SD) or number (percentage)
Age (years) ($n = 88$)	44 (8)
Male gender	17/88 (19%)
Height (cm) ($n = 88$)	171 (9)
Weight (kg) ($n = 88$)	123 (18)
Body mass index (kg/m^2) ($n = 88$)	42.0 (3.6)
Daily smoking	18/88 (21%)
Working	68/87 (78%)
Married/cohabitant	65/76 (86%)
Hypertension	29/85 (34%)
Diabetes mellitus	14/86 (16%)
Myocardial infarction	2/86 (2%)
Stroke	3/86 (4%)
Fibromyalgia	20/87 (23%)
Minor psychiatric disorders	18/87 (21%)
Allergic rhinitis	13/86 (15%)
Chronic obstructive pulmonary disorder	2/85 (2%)
Hypothyroidism	13/85 (15%)
Fibromyalgia	20/87 (23%)

Table 2: Number (proportion) of subjects with irritable bowel syndrome (IBS) before and after the weight loss intervention.

	IBS after intervention	Without IBS after intervention	Sum
IBS before intervention	10 (11.4%)	14 (15.9%)	24 (27.3%)
Without IBS before intervention	7 (8.0%)	57 (64.7%)	64 (72.7%)
Sum	17 (19.3%)	71 (80.7%)	88 (100%)

Prevalence of IBS before intervention is 27.3% and after intervention is 19.3%. Difference between before and after intervention is 8.0% (Newcombe 95% CI −18.2% to 2.4%). McNemar's asymptotic p value is 0.126.

The improvement in IBS-SSS was associated with an improved sense of humour (pc = 0.30; $p = 0.012$) and was negatively associated with improvement in BMI (pc = −0.29; $p = 0.012$). The improvement in GSRS-IBS was associated with improvement in emotional well-being (pc = 0.23; $p = 0.038$) and vitamin D in plasma (pc = 0.29; $p = 0.010$). Neither the changes in IBS-SSS nor GSRS-IBS were significantly associated with the changes in the other health scores or blood tests. None of the associations between improvements remained significant after adjustment for multiple testing (Table 6).

4. Discussion

4.1. Effects of the Intervention. Nineteen out of 25 variables improved significantly during the weight loss intervention, including 9 out of 13 health scores. IBS-SSS and GSRS-IBS, the health scores that measure bowel symptoms, were two of the variables that improved. Subscales of GSRS-IBS

Table 3: Subjects' characteristics before and after the weight loss intervention with analyses of the changes.

	Before intervention		After intervention		Change during the intervention	
		n		*n*	*p* values	*n*
Body mass index (kg/m^2)	42.0 (3.6)	88	38.7 (3.5)	87	**<0.001**$^{\#}$	87
Weight	123 (18)	88	113 (17)	87	**<0.001**$^{\#}$	87
Irritable bowel syndrome (IBS)	24/88 (27%)		17/88 (19%)		0.19$^{\text{¤}}$	
Constipation	5/24 (21%)		4/17 (24%)		0.45$^{\&}$	
Diarrhoea	8/24 (33%)		7/17 (41%)			
Mixed	11/24 (46%)		6/17 (35%)			
Unsubtyped	0/24 (0%)		0/17 (0%)			
Functional constipation	3/88 (3%)		8/88 (9%)		0.23$^{\text{¤}}$	
Functional diarrhoea	3/88 (3%)		3/88 (3%)		1.00$^{\text{¤}}$	
Functional bloating	14/87 (16%)		11/87 (13%)		0.66$^{\text{¤}}$	
IBS-severity scoring system (IBS-SSS)	116 (104)	84	81 (84)	81	**0.001***	77
Gastrointestinal Symptom Rating Scale-irritable bowel syndrome (GSRS-IBS) version	1.8 (0.8)	85	1.6 (0.6)	88	**0.006***	85
Pain syndrome	1.9 (1.1)	85	1.7 (0.9)	88	0.18*	85
Bloating syndrome	2.2 (1.3)	85	1.7 (0.9)	88	**0.001***	85
Constipation syndrome	1.5 (0.9)	85	1.8 (1.2)	88	**0.03***	85
Diarrhoea syndrome	1.8 (0.9)	85	1.5 (0.7)	88	**0.02***	85
Satiety	1.6 (1.1)	85	1.2 (0.5)	88	**0.001***	85
Hopkins Symptom Checklist (HSCL-10)	1.6 (0.5)	88	1.4 (0.5)	88	**<0.001***	88
WHO-5 Well-Being Index (WHO-5)	56 (19)	88	65 (14)	88	**<0.001**$^{\#}$	88
Rosenberg's Self-Esteem Scale	2.8 (0.5)	87	3.0 (0.5)	86	**0.001**$^{\#}$	85
Fatigue Severity Scale (FSS)	37 (15)	87	34 (14)	86	**0.001**$^{\#}$	85
Epworth Sleepiness Scale	8 (5)	88	7 (5)	87	**<0.001***	87
Sense of Humour Questionnaire	3.2 (0.4)	87	3.3 (0.4)	87	0.14*	86
Musculoskeletal pain score	4.5 (3)	87	3.4 (3)	87	**<0.001***	86
Physical activity score	4.3 (0.2)	88	4.8 (2.2)	88	0.12*	88
Food tolerance (Suter)	24.0 (2.5)	85	24.2 (2.2)	88	0.47*	85
Number of meals/day	4.0 (1.0)	82	4.7 (1.1)	82	**<0.001***	82
LDL (1.5–4.8 mmol/L)	3.3 (0.9)	87	2.8 (0.8)	84	**<0.001**$^{\#}$	84
HDL (F: 1.0–2.7 mmol/L; M: 0.8–2.1 mmol/L)	1.2 (0.3)	87	1.1 (0.3)	85	**<0.001***	84
Cholesterol (3.3–6.9 mmol/L)	5.1 (1.0)	87	4.3 (0.9)	85	**<0.001**$^{\#}$	84
CRP (<5 mg/L)	7 (6)	87	4 (4)	87	**<0.001***	86
HbA1c (4.0–6.0%)	5.8 (1.1)	87	5.5 (0.8)	85	**<0.001***	84
TSH (0.27–4.20 mIE/L)	1.9 (1.1)	87	1.6 (1.1)	85	**0.002***	84
T_4 (12–22 pmol/L)	15 (3)	87	17 (7)	85	**<0.001***	84
Vitamin B_1 (95–200 nmol/L)	156 (23)	87	163 (30)	85	0.10*	84
Vitamin B_6 (15–160 nmol/L)	33 (32)	86	62 (44)	85	**<0.001***	83
Vitamin B_{12} (140–600 pmol/L)	364 (162)	87	433 (231)	85	**<0.001***	84
Vitamin D (50–150 nmol/L)	55 (21)	87	61 (26)	85	**0.009**$^{\#}$	84

The values are given as mean (SD) or *n* (%). LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; TSH: thyroid-stimulating hormone; T_4: thyroxin. Statistical tests with $^{\text{¤}}$McNemar's test, $^{\&}$Stuart-Maxwell test, *Wilcoxon signed rank test, or $^{\#}$paired *t*-test.

showed that bloating, satiety, and diarrhoea were relieved, while constipation worsened. The prevalence of IBS was reduced, but not significantly. It was the subjects with IBS at inclusion who had the most marked improvement in bowel symptoms. In this group, the whole confidence interval for the IBS-SSS improvement was above the limit for a clinically significant effect. Subjects without IBS at inclusion did not have significant changes in IBS-SSS and GSRS-IBS.

BMI was reduced by 3.3 kg/m^2, achieved by a conservative weight loss intervention based on lifestyle changes with dietary modifications and increased physical activity. The frequent follow-up in groups, the clear expectations from the health care personnel, and the information that

Table 4: Subjects' characteristics before and after the conservative weight loss intervention, stratified by IBS status before the intervention.

	Subjects with IBS						Subjects without IBS						
	Before intervention	n	After intervention	n	Change during the intervention p values	n	Before intervention	n	After intervention	n	Change during the intervention p values	n	Differences in changes between subjects with and without IBS p values
IBS-severity scoring system (IBS-SSS)	218 (89)	24	132 (83)	21	**<0.001***	21	75 (79)	60	63 (77)	60	0.23*	56	**<0.001**#
Gastrointestinal Symptom Rating Scale-irritable bowel syndrome version (GSRS-IBS)	2.6 (0.7)	24	2.0 (0.7)	24	**0.001***	24	1.5 (0.6)	61	1.5 (0.6)	64	0.57*	61	**<0.001**#
Pain syndrome	3.0 (1.0)	24	2.2 (1.1)	24	**0.01***	24	1.4 (0.7)	60	1.5 (0.8)	64	0.29*	60	**0.001**#
Bloating syndrome	3.2 (1.3)	24	2.1 (1.0)	24	**0.003***	24	1.8 (1.0)	61	1.6 (0.8)	64	0.06*	61	**0.018**#
Constipation syndrome	1.9 (1.3)	24	2.3 (1.5)	24	0.32*	24	1.3 (0.6)	61	1.6 (1.1)	64	**0.03***	61	0.81#
Diarrhoea syndrome	2.5 (1.1)	24	1.9 (1.0)	24	**0.006***	24	1.5 (0.7)	61	1.4 (0.6)	64	0.46	61	**0.010**#
Satiety	2.2 (1.5)	24	1.4 (0.6)	24	**0.012***	24	1.4 (0.7)	61	1.2 (0.5)	64	**0.03***	61	0.053#
Number of meals/day	4.1 (0.9)	23	4.5 (1.1)	22	0.26*	21	3.9 (1.0)	62	4.8 (1.1)	62	**<0.001***	61	**0.015**#
Hopkins Symptom Checklist (HSCL-10)	1.9 (0.6)	24	1.6 (0.6)	24	0.002*	24	1.5 (0.5)	64	1.4 (0.5)	64	**0.006**	64	**0.044**#

The values are given as mean (SD) or n (%). All variables from Table 3 where the change is significantly different in subjects with and without IBS are included in this table. Statistical tests with *Wilcoxon signed rank test and #Mann-Whitney U test.

Table 5: Comparison of intake of energy, bread and milk, before and during the last three weeks of the intervention.

	Measured before the intervention						Recommended during the intervention
	All subjects	n	Subjects with IBS	n	Subjects without IBS	n	
Energy (kJ)	10,458 (3890)	68	11,778 (4377)	19	9949 (3601)	49	3765
Intake of milk (ml)	276 (0–1791)	68	304 (5–1791)	19	276 (0–1422)	49	450
Intake of bread (g)	156 (24–338)	68	170 (54–338)	19	165 (24–276)	49	144

Results are given as mean (standard deviation) or median (range) depending on the distribution. The food intake before the intervention was registered with food frequency questionnaires and is presented next to the specific recommendations, given the last three weeks of the intervention.

good compliance was a prerequisite for bariatric surgery in the public health system after the intervention were crucial for the satisfactory results.

According to the recommendations in the program, the number of meals per day increased. Lower energy intake and a healthier choice of macronutrients (less saturated fats and sugar) were probable causes of the reductions in serum cholesterol and low-density lipoprotein [36]. Healthier food could explain parts of the increase in serum vitamin levels. Vitamin D levels might also have increased due to sun exposure related to outdoor activities and reduced fat mass [37]. Reduced secretion of adipokines from the visceral adipose tissue and some increase in physical activity account for the expected fall in CRP values [38]. Psychological effects related to the successful weight loss, the social support, and some increase in physical activity were probably important causes of the improved psychological distress, subjective well-being, self-esteem, fatigue, sleepiness, and musculoskeletal pain.

4.2. Variables Associated with Bowel Symptom Improvement. The second part of the analysis aimed to identify associations between changes in bowel symptoms and changes in other variables. The social support and positive psychosocial environment achieved during the intervention is a likely explanation for the association between improved bowel symptoms and improvement in subjective well-being and sense of humour. Psychosocial factors are of importance for the symptom load in subjects with IBS [9].

The negative association between the improvements in IBS-SSS and BMI was unexpected. The diet in this specific conservative weight loss program was based on FODMAP-rich food (rye-based crisp bread, milk, and vegetables as cauliflower and peas). Even though energy intake was heavily reduced, absolute intake of the main FODMAP sources in a Norwegian diet was mainly unchanged. The relative amount of FODMAPs in the food was therefore increased, especially in subjects with strict adherence to recommendations, which might be an explanation of the negative association between improvement in bowel symptoms and BMI.

Reduction of GSRS-IBS was associated with an increase in serum vitamin D, and the improvements in bowel symptoms could be related to other changes in diet, such as more regular eating of high-quality food rich in micronutrients. Changes in CRP were not associated with changes in bowel symptoms. Seen together with the observation that

Table 6: Associations between the improvement in bowel symptoms and the improvement in the other variables.

	IBS-severity scoring system (IBS-SSS)				Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) version			
	B (95% CI)	pc	*p* value	*q* value	*B* (95% CI)	pc	*p* value	*q* value
Male gender	15.1 (−30.8; 61.1)	0.08	0.51		−0.01 (−0.38; 0.35)	0.01	0.95	
Age	1.8 (−0.3; 3.9)	0.19	0.094		0.012 (−0.005; 0.029)	0.15	0.18	
Body mass index	**−15.2 (−27.0; −3.5)**	**−0.29**	**0.012**	0.13	−0.07 (−0.17; 0.03)	−0.15	0.18	0.48
HSCL-10	23.5 (−26.9; 74.1)	0.11	0.36	0.97	0.28 (−0.11; 0.68)	0.16	0.15	0.48
WHO-5	1.3 (−0.1; 2.6)	0.22	0.059	0.43	**0.011 (−0.001; 0.021)**	**0.23**	**0.038**	0.42
Self-esteem	42.8 (−13.1; 98.7)	0.18	0.13	0.79	0.12 (−0.31; 0.54)	0.06	0.58	0.79
FSS	0.68 (−1.34; 2.69)	0.08	0.51	0.97	0.003 (−0.013; 0.019)	0.04	0.70	0.79
Sleepiness	−0.26 (−5.46; 4.94)	−0.01	0.92	0.97	0.02 (−0.022; 0.062)	0.10	0.35	0.60
Sense of humour	**74.7 (17.9; 131.4)**	**0.30**	**0.012**	0.13	0.35 (−0.11; 0.81)	0.17	0.14	0.48
Musculoskeletal pain	0.18 (−0.20; 9.55)	0.01	0.97	0.97	0.012 (−0.061; 0.084)	0.04	0.75	0.79
Physical activity	4.09 (−3.15; 11.33)	0.13	0.26	0.73	−0.013 (−0.068; 0.043)	−0.05	0.65	0.79
Number of meals/day	0.05 (−0.07; 0.16)	0.09	0.44	0.97	0.11 (−0.03; 0.01)	0.16	0.16	0.48
Food tolerance	3.02 (5.67; 11.70)	0.08	0.49	0.97	0.04 (−0.03; 0.10)	0.12	0.31	0.60
LDL	8.8 (−24.8; 42.4)	0.06	0.60	0.97	0.10 (−0.17; 0.37)	0.08	0.46	0.72
HDL	−11.0 (−110.6; 88.6)	−0.03	0.83	0.97	−0.75 (−1.54; 0.04)	−0.21	0.061	0.45
Cholesterol	3.0 (−26.4; 32.4)	0.03	0.84	0.97	0.12 (−0.13; 0.36)	0.11	0.35	0.60
CRP	−0.4 (−4.7; 4.0)	−0.02	0.87	0.97	0.003 (−0.033; 0.039)	0.02	0.87	0.87
HbA1c	−8.2 (−40.9; 24.4)	−0.06	0.62	0.97	−0.08 (−0.35; 0.19)	−0.07	0.54	0.79
TSH (decrease)	3.1 (−15.2; 21.4)	0.04	0.74	0.97	0.02 (−0.12; 0.17)	0.04	0.74	0.79
T_4 (increase)	0.7 (−2.2; 3.6)	0.06	0.63	0.97	0.004 (−0.020; 0.028)	0.04	0.75	0.79
Vitamin B_1	0.24 (−0.51; 0.99)	0.08	0.53	0.97	0.005 (−0.001; 0.011)	0.17	0.13	0.48
Vitamin B_6	−0.01 (−0.49; 0.47)	−0.01	0.97	0.97	0.002 (−0.002; 0.006)	0.14	0.23	0.51
Vitamin B_{12}	−0.01 (−0.15; 0.14)	−0.01	0.91	0.97	0.0005 (0.0003; 0.0014)	0.14	0.21	0.51
Vitamin D	0.52 (−0.43; 1.46)	0.13	0.28	0.97	**0.010 (−0.002; 0.017)**	**0.29**	**0.010**	0.22

HSCL-10: Hopkins Symptom Checklist 10; WHO-5: World Health Organization 5 Well-Being Index; FSS: Fatigue Severity Scale; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; TSH: thyroid-stimulating hormone; T_4: thyroxin. Linear regression with IBS-SSS and GSRS-IBS as the independent variables, and the other variables one by one as covariates, adjusted for gender and age (gender and age presented unadjusted in the first two rows). *q* values are Benjamini-Hochberg adjusted to preserve false discovery rate for twenty-two hypotheses.

weight loss itself was negatively correlated with bowel symptom improvement, our data do not support the hypothesis that systemic low-grade inflammation from adipose tissue is the main mediator that leads to IBS in the obese [18]. However, the observed improvement might be due to interplay between several peripheral factors. For instance, the gut microbiota is associated with both IBS and MO [16, 17], and the interaction between peripheral gut factors as food, microbiota, and local gut inflammation could plausibly change gut symptoms.

4.3. Clinical Implications. Improvement in BMI and many health scores and biomarkers was observed, and the study adds to the evidence that a conservative weight loss program can lead to better health in the short term [22]. Comorbidity should be taken into account when choosing between treatment alternatives for subjects with MO [19]. This study indicates that when MO and IBS coexist, nonsurgical treatment should be considered, as surgery-induced weight loss probably leads to increased abdominal pain and bowel symptoms [5, 39].

The degree of improvement in IBS-SSS from this lifestyle intervention in subjects with IBS and MO was comparable to the improvement seen after IBS-specific diets in normal weight subjects [24]. It is probable that the effect of conservative weight loss intervention on bowel symptoms can be made even larger if FODMAPs are taken into account.

4.4. Strengths and Limitations. The weight loss program has been developed and used with favorable experience for a long time in several Norwegian clinics for morbid obesity [22]. The program functioned well, and the loss to follow-up during the six-month period was low. The amount of weight change achieved by the subjects was satisfactory, and the study was large enough to show a statistically and clinically significant improvement in bowel symptoms and many other variables. Validated instruments were used for the measurements of the bowel symptoms and the health-related variables [8, 23, 25–30, 32].

Intake of FODMAPs was not measured in individual participants after the intervention, and registration of upper gastrointestinal disorders was not done. Fat distribution was

not measured with either waist/hip ratio or radiological methods, and the compliance with advice (diet and physical activity) given during the intervention was unknown. None of the associations between changes remained significant after adjustment for multiple testing, which limits the strength of the findings. The generalizability of the results to subjects with BMI under 35 is unknown. The Rome III criteria demand symptoms of at least six months duration to diagnose IBS, which limits the diagnosis of IBS in subjects with new symptoms. A longer study period had been preferable.

5. Conclusions

BMI was reduced and health improved during a conservative weight loss program for subjects with MO. Subjects with IBS and MO also experienced a clinically significant improvement in IBS symptoms. As bowel symptoms often aggravate after bariatric surgery, conservative treatment should be considered as an alternative in subjects with MO and IBS if medically advisable. Psychosocial changes and possibly a more healthy and regular diet could explain the improvement in bowel symptoms.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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Appendix 4: Case report form

CRF – Prosjekt overvekt: Kontroll preoperativt ☐; 6 mnd ☐; 12 mnd ☐; Pas nr. ☐☐☐

UiO – kostregistrering nr. ☐☐☐☐☐

Medisinske opplysninger

for

Fornavn – Mellomnavn – Etternavn

☐☐-☐☐-☐☐-☐☐☐☐

Personnummer

Adresse: _____

_____

Postnummer: _____ Sted: _____

Tlf (fast): _____

Tlf (mobil): _____

CRF – Prosjekt overvekt: Kontroll preoperativt ☐; 6 mnd ☐; 12 mnd ☐; Pas nr. ☐☐☐

Dato: ☐☐-☐☐-☐☐☐☐ Kjønn: Mann ☐ Kvinne ☐ Alder: ☐☐ år

Høyde: ☐☐☐ cm. Vekt ☐☐☐,☐ kg . Livvidde ☐☐☐ cm. Hoftevidde ☐☐☐ cm

Etnisk bakgrunn:

Norge: ☐ Norden (untatt Norge): ☐ Vest-Europa (unntatt Norden): ☐

Øst-Europa: ☐ Asia: ☐ Afrika: ☐ Amerika: ☐

Familie og venner:

Bor du sammen med noen: Ja ☐ Nei ☐

Hvis JA: Ektefelle/samboer Ja ☐ Nei ☐

Andre personer, 18 år og eldre Ja ☐ Nei ☐

Personer under 18 år: Ja ☐ Nei ☐

Utdannelse og arbeid:

Hvor mange års skolegang har du gjennomført: Antall år: ☐☐

Er du i inntektsgivende arbeid: Ja, full tid: ☐ Ja, deltid: ☐ Nei: ☐

Spørsmål om mat, drikke, nytelsesmidler og fysisk aktivitet:

Kaffe/te: Hvor mange kopper kaffe/te drikker du daglig? (sett 0 hvis du ikke drikker kaffe/te daglig)
Antall kopper kaffe pr dag: ☐☐ Antall kopper te pr dag: ☐☐

Alkoholvaner: Hvor ofte har du i løpet av det siste året drukket alkohol? (lettøl regnes ikke med)

4-7 ganger pr uke: ☐ 2-3 ganger pr uke: ☐ ca 1 gang pr uke: ☐ 2-3 ganger pr måned: ☐
Omtrent 1 gang pr måned: ☐ Noen få ganger siste år: ☐ Har ikke drukket alkohol siste år: ☐

Røykevaner: Har du røkt/røyker du daglig: Ja nå: ☐ Ja, tidligere: ☐ Aldri: ☐

Fysisk aktivitet: Hvordan har din fysiske aktivitet i fritiden vært det siste året:

	Timer pr uke			
	Ingen	Under 1	1-2	3 og mer
Lett aktivitet (ikke svett / andpusten)	☐	☐	☐	☐
Hard aktivitet (svett / andpusten)	☐	☐	☐	☐

CRF – Prosjekt overvekt: Kontroll preoperativt ☐; 6 mnd ☐; 12 mnd ☐; Pas nr. ☐☐☐

Spørsmål om egen helse:

Hvordan er helsen din nå? (sett bare ett kryss)

Dårlig: ☐ Ikke helt god: ☐ God: ☐ Svært god: ☐

Har du, eller har du hatt følgende sykdommer:

	Ja	Nei		Ja	Nei
Astma	☐	☐	Fibromyalgi/kronisk smertesyndrom	☐	☐
Høysnue	☐	☐	Psykiske plager som du har søkt hjelp for	☐	☐
Kronisk bronkitt/emfysem	☐	☐	Hjerteinfarkt	☐	☐
Diabetes (sykkersyke)	☐	☐	Angina pectoris (hjertekrampe)	☐	☐
Benskjørhet (osteoporose)	☐	☐	Hjerneslag / hjerneblødning (drypp)	☐	☐
Høyt stoffskifte (hyperthyreose)	☐	☐	Gallesten eller annen galleveissykdom	☐	☐
Lavt stoffskifte (hypothereose)	☐	☐	Høyt blodtrykk	☐	☐
Polycystisk ovariesyndrom	☐	☐	Mage-tarm sykdom *	☐	☐

Hvis du har svart Ja på spørsmålet om mage-tarm sykdom – angi navn/type mage-tarm sykdom:

Hvis du har eller har hatt andre sykdommer – vennligst skriv det her:

Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 4 ukene?

	Ikke plaget	En del plaget	Sterkt plager
Nakke/skyldre	☐	☐	☐
Armer, hender	☐	☐	☐
Øvre del av ryggen	☐	☐	☐
Korsryggen	☐	☐	☐
Hofter, ben, føtter	☐	☐	☐
Andre steder	☐	☐	☐

Spørsmål om trivsel og velvære (WHO-5)

Ved å svare på spørsmålene nedenfor kan du gi oss et bilde av hvor bra eller dårlig du føler deg for tiden.

Vennligst sett **en sirkel rundt det svaret som passer best** for hver uttalelse om hvordan du for det meste har følt deg gjennom de siste to ukene.

Legg merke til at høyere tall betyr bedre trivsel og velvære.

Eksempel: Hvis du det meste av tiden i de siste to ukene har følt deg glad og i godt humør, setter du en sirkel rundt tallet 4 på linjen ved siden av dette spørsmålet.

I de siste to ukene har jeg …….	Hele tiden	Det meste av tiden	Mer enn halve tiden	Mindre enn halve tiden	Av og til	Aldri
Følt meg glad og i godt humør	5	4	3	2	1	0
Følt meg rolig og avslappet	5	4	3	2	1	0
Følt meg aktiv og sterk	5	4	3	2	1	0
Følt meg opplagt og uthvilt når jeg våkner	5	4	3	2	1	0
Følt at mitt daglige liv har vært fylt av ting som interesserer meg	5	4	3	2	1	0

Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken ? (HSC10)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engestelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht framtida	☐	☐	☐	☐

Følelse av å være sliten / utmattet (Fatigue)

Sett en ring rundt det tallet som passer best for deg. Jo bedre du synes utsagnet passer overens med hvordan du føler deg jo høyre skår:
Lavt tall = helt uenig
Høyt tall = helt enig

Siste uke har jeg følt at……	**Skår**						
1. Mitt pågangsmot blir dårligere når jeg er utmattet	1	2	3	4	5	6	7
2. Jeg blir fort utmattet ved anstrengelser	1	2	3	4	5	6	7
3. Jeg har lett for å bli utmattet	1	2	3	4	5	6	7
4. Utmattelse nedsetter min fysiske funksjonsevne	1	2	3	4	5	6	7
5. Utmattelse skaper ofte problemer for meg	1	2	3	4	5	6	7
6. Utmattelse fører til at jeg har dårlig fysisk utholdenhet over lengre tid	1	2	3	4	5	6	7
7. Utmattelse virker negativt inn på mine gjøremål og forpliktelser	1	2	3	4	5	6	7
8. Utmattelse er ett av mine tre mest plagsomme symptomer	1	2	3	4	5	6	7
9. Utmattelse virker negativt inn på mitt arbeid, min familie og mitt øvrige sosiale liv	1	2	3	4	5	6	7

Her følger noen påstander. Les hvert utsagn nøye og kryss av for de svarene som best angir hvordan du oppfatter deg selv akkurat nå. (Rosenberg self esteem)

	Veldig enig	Enig	Uenig	Veldig uenig
I det store og hele er jeg fornøyd med meg selv.				
Av og til synes jeg at jeg ikke er noe tess i det hele tatt.				
Jeg synes jeg har mange gode kvaliteter.				
Jeg synes ikke jeg har mye å være stolt av.				
Jeg kan utføre ting like bra som andre folk.				
Av og til føler jeg meg virkelig unyttig.				
Jeg mener at jeg er verd noe, i alle fall like bra som andre.				
Jeg skulle ønske jeg hadde selvrespekt.				
Jeg tenker positivt om meg selv.				
Stort sett har jeg en tendens til å føle at jeg er mislykket.				

Søvnighet. (Epworth søvnighetsskala)

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner, i motsetning til kun å føle deg trett? Spørsmålene gjelder din vanlige måte å reagere på.

Selv om du ikke har gjort noe at dette den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg. Bruk følgende skala:

0 = ville **aldri** døse/sovne
1 = en **liten sjanse** for å døse/sovne
2 = **moderat sjanse** for å døse/soven
3 = **stor sjanse** for å døse/sovne
Besvar hvert spørsmål så riktig som mulig – marker svaret med et kryss i ruten som passer best.

Situasjon	**0**	**1**	**2**	**3**
Sitte å lese				
Se på TV				
Sitte, inaktiv på et offentlig sted (f.eks. på teater eller et møte)				
Som passasjer på en en-times biltur uten pause				
Legge deg til å hvile om ettermiddagen hvis omstendighetene tillater det				
Sitte å snakke med noen				
Sitte stille etter lunsj (uten å ha inntatt alkohol)				
I en bil som har stoppet for noen få minutter i trafikken				

Humor:

Svare ved å sette et kryss i ruten bak det alternativet som best gir uttrykk for din generelle holdning.

1) Oppfatter du lett et hint (blunk med øyet, en lett endring av tonefallet) som forsøk på en morsomhet?
Svært lett ☐ Ganske lett ☐ Ganske vanskelig ☐ Svært vanskelig ☐

2) Ville det være lett for deg å finne noe komisk eller vittig i de fleste situasjoner?
Svært lett ☐ Ganske lett ☐ Ganske vanskelig ☐ Svært vanskelig ☐

3) Det er noe ansvarsløst og upålitelig over folk som stadig prøver å være morsomme.
Helt uenig ☐ Ganske uenig ☐ Ganske enig ☐ Helt enig ☐

4) Det som irriterer meg mest med humorister, er at de så tydelig nyter sin evne til å få andre til å le.
Helt uenig ☐ Ganske uenig ☐ Ganske enig ☐ Helt enig ☐

5) Vil du si at du opplever mange grunner til munterhet i løpet av en vanlig dag?
Svært mange ☐ Ganske mange ☐ Ganske få ☐ Svært få ☐

6) Det er mitt inntrykk at de som prøver å være morsomme, gjør det for å skule sin mangel på selvtillit.
Nei, slett ikke ☐ I noen grad ☐ Ganske riktig ☐ Helt riktig ☐

CRF – Prosjekt overvekt: Kontroll preoperativt ☐; 6 mnd ☐; 12 mnd ☐; Pas nr. ☐☐☐

Matintoleranse (Suters spørreskjema)

Spørsmålene som følger gjelder dine matvaner og om du tåler all slags mat.

Hvor fornøyd er du alt i alt med hva du kan spise:

Veldig godt fornøyd: ☐ Godt fornøyd: ☐ Sånn passe: ☐ Litt misfornøyd: ☐ Svært misfornøyd: ☐

Hvor mange måltider spiser du om dagen: ☐☐

Hvilke måltider er det (sett et kryss for hvert måltidene du spiser):

Frokost: ☐ Lunsj: ☐ Middag: ☐ Kveldsmat: ☐

Spiser du mellom måltidene: Ja: ☐ Nei: ☐

Hvis ja – når? Om morgenen: ☐ Om ettermiddagen: ☐ Om kvelden: ☐

Kan du spise hva som helst uten problemer/ubehag? Ja: ☐ Nei: ☐

Hvis du har svart nei – hva er det som er vanskelig å spise:

Rødt kjøtt	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Hvitt kjøtt	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Salat	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Grønnsaker	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Brød	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Ris	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Pasta	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Fisk	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐
Melk	Lett å spise ☐	Litt problemer ☐	Kan ikke spise det ☐

Plages du av oppkast eller oppstøt/oppgulp:

Daglig ☐ Ofte (mer enn 2 ganger pr uke) ☐ Sjelden ☐ Aldri ☐

Mageplager

Har du siste 6 måneder hatt plager fra magen slik som smerter, ubehag, forstoppelse, diaré, sure oppstøt, halsbrann, oppkast, luftplager, oppblåsthet eller annet: Ja ☐ Nei ☐

Hvis JA – svar på alle spørsmålene som kommer. Hvis NEI – avslutt skjemaet her

Hvis JA – tror du plagene skyldes maten du spiser?	Ja ☐	Nei ☐
Får du vondt av all slags mat (uansett hva du spiser)	Ja ☐	Nei ☐
Er det spesielle matslag som gir mer plager	Ja ☐	Nei ☐

Får du plager av **MELK / MEIERIPRODUKTER**? (Finnes ofte i ost, margarin og smør, krem, kaker, vafler pannekaker, risgrøt, pølser, kjøttkaker og –pudding, fiskekaker, pizza, sauser, supper):

Ja ☐ Nei ☐

Hvis JA – hvor sikker er du på at melk / meiereprodukter utløser plagene:
Marker et kryss på streken hvor sikker du er på at plagene skyldes melk/meieriprodukter

Helt sikker på at mageplagene ikke er relatert til inntak av melk/ meieriprodukter — Helt sikker på at mageplagene er relatert til inntak av melk/ meieriproduketer

Får du plager av **HVETE**? (Finnes brød, rundstykker og annen gjærbakst, og i pannekaker, kaker, kjeks, knekkebrød, flatbrødgjærbakst, panering, müsli, kjøttfarseprodukter, fiskefarseprodukter, pasta)

Ja ☐ Nei ☐

Hvis JA – hvor sikker er du på at hvete-produkter utløser plagene:
Marker et kryss på streken hvor sikker du er på at plagene skyldes hveteprodukter

Helt sikker på at mageplagene ikke er relatert til inntak av hvete — Helt sikker på at mageplagene er relatert til inntak av hvete

Får du plager av **EGG**? (finnes ofte i pannekaker, kaker, omelett, panering, majones, pasta)

Ja ☐ Nei ☐

Hvis JA – hvor sikker er du på at egg og egg-produkter utløser plagene:
Marker et kryss på streken hvor sikker du er på at plagene skyldes hveteprodukter

Helt sikker på at mageplagene ikke er relatert til inntak av egg — Helt sikker på at mageplagene er relatert til inntak av egg

Nevn andre matslag du mener utløser dine mageplager:

Beskrivelse av dine mageplager:

	RING RUNDT TALLET som best beskriver dine mageplager	
1. Hvor ofte har du hatt ubehag eller smerte i mageregionen de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Gå til spørsmål 9***
2. For kvinner: Har du hatt dette ubehaget eller denne smerten kun under menstruasjon og ikke på andre tidspunkt?	0. Nei 1. Ja 2. Gjelder ikke for meg da jeg er forbi overgangsalderen (menopause) eller jeg er mann	
3. Har du hatt dette ubehaget eller disse smertene i 6 måneder eller mer?	0. Nei 1. Ja	
4. Hvor ofte har ubehaget eller smerten blitt bedre eller helt borte etter at du har hatt avføring?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
5. Hadde du oftere avføring da ubehaget eller smerten begynte?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	

6. Hadde du sjeldnere avføring da ubehaget eller smerten begynte?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
7. Hadde du løsere avføring da ubehaget eller smerten begynte?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
8. Hvor ofte hadde du hardere avføring da ubehaget eller smerten begynte?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
9. Hvor ofte har du hatt mindre enn tre avføringer (0-2) i uken de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
10. Hvor ofte har du hatt hard eller klumpete avføring de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	

11. Hvor ofte har du måttet presse hardt for å få avføring de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
12. Hvor ofte har du følt at du ikke har fått tømt tarmen helt de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
13. Hvor ofte har du følt at tarmtømmingen har blitt hindret (blokkert) de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
14. Hvor ofte har du vært nødt til å trykke på eller rundt endetarmsåpningen eller fjerne avføring for å bli ferdig med å tømme tarmen de siste 3 månedene?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
15. Begynte noen av symptomene på forstoppelse, nevnt i spørsmålene 9-14, for mer enn 6 måneder siden?	0. Nei 1. Ja	

16. Hvor ofte har du hatt løs, grøtaktig eller vandig avføring de siste 3 månedene?	0. Aldri eller sjelden → 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	***Gå til spørsmål 19***
17. Har minst tre av fire (3/4) av avføringene dine vært løse, grøtaktige eller vandige de siste 3 månedene?	0. Nei 1. Ja	
18. Begynte de hyppige, løse, grøtaktige eller vandige avføringene for mer enn 6 måneder siden?	0. Nei 1. Ja	
19. Hvor ofte har du vært oppblåst eller utspilt de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Gå til spørsmål 21***
20. Begynte symptomene på oppblåsthet eller utspilthet for mer enn 6 måneder siden?	0. Nei 1. Ja	

21. Hvor ofte har du følt deg ubehagelig mett etter et måltid av normal størrelse de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Gå til spørsmål 23***
22. Har du hatt denne ubehagelige mettheten etter måltider i 6 måneder eller mer?	0. Nei 1. Ja	
23. Hvor ofte har du ikke klart å spise et måltid av normal størrelse de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Gå til spørsmål 25***
24. Har du hatt denne manglende evnen til å spise et måltid av normal størrelse i 6 måneder eller mer?	0. Nei 1. Ja	
25. Hvor ofte har du hatt smerte eller en brennende følelse midt i magen og over navlen, men ikke i brystet, de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Ikke svar spørsmål 26***

26. Har du hatt denne smerten eller brennende følelsen i 6 måneder eller mer?	0. Nei 1. Ja	
Funksjonelle magesmerter		
1. Hvor ofte har du hatt smerte eller ubehag midt i brystet i løpet av de siste 3 månedene?	0. Aldri 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	
2. Hvor ofte har du hatt brystbrann (et brennende ubehag eller brennende smerte i brystet) i løpet av siste 3 måneder?	0. Aldri 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	
3. Hvor ofte har du hatt smerte eller et brennende ubehag midt i magen og over navlen, men ikke i brystet de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Gå til spørsmål 5***
4. Har du hatt denne smerten eller brennende ubehag i 6 måneder eller mer?	0. Nei 1. Ja	

5. Hvor ofte har du hatt ubehag eller smerte i mageregionen de siste 3 månedene?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Hopp over spørsmålene 6 - 19***
6. Har du hatt bare smerter (ikke ubehag eller en blanding av ubehag og smerte)?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
8. Hvor ofte begrenset eller umuliggjorde denne smerten dine daglige aktiviteter (f.eks. arbeid, huslige gjøremål, sosiale aktiviteter)?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
10. Hendte det at denne smerten eller brennende ubehag oppsto og ble helt borte i løpet av samme dag?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
11. Hvor alvorlig var vanligvis smerten eller det brennende ubehag du hadde midt i magen og over navlen.	1. Veldig mild 2. Mild 3. Moderat 4. Alvorlig	

	5. Veldig alvorlig	
12. Ble smerten eller det brennende ubehaget påvirket av å spise?	0. Ikke påvirket av å spise. 1. Ble verre av å spise. 2. Ble bedre av å spise	
13. Ble smerten eller det brennende ubehaget bedre eller helt borte etter tarmtømming eller luftavgang?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
14. Hadde du en endring i antall tarmtømminger (enten flere eller færre) da smertene eller det brennende ubehaget startet?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
15. Hadde du vanligvis hardere eller løsere avføring da smertene eller det brennende ubehaget startet?	0. Aldri eller sjelden 1. Av og til 2. Ofte 3. Nesten alltid 4. Alltid	
16. Hvor ofte har du siste 3 måneder hatt verk, smerte eller tykk i endetarmen eller endetarmåpningen når du ikke skulle ha tarmtømming?	0. Aldri → 1. Mindre enn en dag i måneden 2. En dag i måneden 3. To til tre dager i måneden 4. En dag i uken 5. Mer enn en dag i uken 6. Hver dag	***Hopp over spørsmålene 17-19***
17. Hvor lenge varte verkingen, smerten	1. Fra sekunder opp til 20 minutter for så å bli helt borte.	

eller trykket?	2. Mer enn 20 minutter og opp til flere dager eller enda lenger.	
18. Oppsto og forsvant smertene i endetarmen eller endetarmsåpningen helt i løpet av samme dag?	0. Nei 1. Ja	
19. Oppsto verkingen, smerten eller trykket i endetarmen eller endetarmsåpningen for mer enn 6 måneder siden?	0. Nei 1. Ja	

Hvordan har du følt deg siste uken

Undersøkelsen inneholder spørsmål om hvordan du har følt deg og hvordan du har hatt det DEN SISTE UKEN. Sett kryss (X) ved det alternativet som passer best på deg og din situasjon.

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

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

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

   ☐ Ingen plager i det hele tatt
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3. Har du i løpet av den siste uken vært plaget av OPPBLÅSTHET?

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- ☐ Alvorlige plager
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4. Har du i løpet av den siste uken vært plaget av LUFTAVGANG?

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- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

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

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

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- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

7. Har du i løpet av den siste uken vært plaget av LØS AVFØRING?

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- ☐ Milde plager
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- ☐ Ganske alvorlige plager
- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

8. Har du i løpet av den siste uken vært plaget av HARD AVFØRING?

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- ☐ Meget alvorlige plager

9. Har du i løpet av den siste uken vært plaget av TVINGENDE AVFØRINGSBEHOV (plutselig behov for å gå på toalettet for å tømme tarmen)?

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10. Har du i løpet av den siste uken vært plaget av en FØLELSE AV UFULLSTENDIG TØMMING AV TARMEN ETTER AVFØRING?

- ☐ Ingen plager i det hele tatt
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- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

11. Har du i løpet av den siste uken vært plaget av at du FØLER DEG METT LIKE ETTER AT DU HAR BEGYNT PÅ ET MÅLTID?

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

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

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- ☐ Alvorlige plager
- ☐ Meget alvorlige plager

CRF – Prosjekt overvekt: Kontroll preoperativt ☐; 6 mnd ☐; 12 mnd ☐; Pas nr. ☐☐☐

MAGEPLAGER: Grad og hyppighet

1. Hvor mange dager har du magesmerter/ubehag i løpet av en 10-dagers periode? For eksempel, hvis du har smerte-episoder 4 av 10 dager skriver du 4. Hvis du har smerter hver dag skriver du 10

   Jeg har smerter _____ dager i løpet av en 10 dagers periode

2. På en skala fra 0 (ingen smerte) til 10 (verst tenkelige smerte), hvor alvorlig er dine smerter vanligvis.

   Mine smerter har følgende alvorlighetsgrad _____ (ett tall mellom 0 og 10).

3. Er smertene konstant til stede (det vil si at du har smerter alltid (hele dagen) og hver eneste dag)?

   Ja ☐ Nei ☐

MAGEPLAGER: Gradert på en annen måte

Har du magesmerter: Ja ☐ Nei ☐

Hvis du har magesmerter – hvor alvorlige er magesmertene dine?

0 %					100%
ingen smerte	lett smerte	moderat smerte	alvorlig smerte	svært alvorlig smerte	

Plages du med luft i magen, oppblåst/svullen mage, stram mage: Ja ☐ Nei ☐

Hvis ja – hvor alvorlige er disse plagene?

0 %				100%
ingen	lette	moderate	alvorlige	svært alvorlige

Hvor fornøyd er du med mage-tarm funksjonen (avføringsmønsteret) din?

0 %			100%
meget fornøyd	ganske fornøyd	litt misfornøyd	svært misfornøyd

Hvordan påvirker / forstyrrer mageplagene livet ditt rent generelt?

0 %			100%
ikke i det hele	ikke mye	ganske mye	svært mye