DIETARY PATTERNS LINKED TO SYMPTOMS IN PATIENTS WITH A DISORDER OF GUT-BRAIN INTERACTION

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“Allt kommer att bli bra” or “Everything will be alright”

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SUMMARY

Disorders of gut-brain interaction (DGBI) encompass a range of medical conditions characterized by gastrointestinal (GI) symptoms, in the absence of alarm features or organic diseases that explain the symptoms, after a minimal relevant clinical evaluation. One of the most common DGBI is irritable bowel syndrome (IBS), characterized by abdominal pain associated with altered bowel habits. As many patients with a DGBI report food-related symptoms, diet has become a prominent focus in DGBI research. The general aim of this thesis was to contribute to the overall understanding of underlying mechanisms of food-related symptoms and optimizing the diagnosis, and management of patients with a DGBI.

Study I provided insights into the global prevalence and burden of meal-related abdominal pain. A significant portion of the general population reported experiencing this type of pain, with frequent sufferers being predominantly females, younger individuals, exhibiting other GI and non-GI symptoms, having a poorer quality of life, and utilizing healthcare services more often. Study II focused on predicting symptom responses the traditional IBS diet and the low FODMAP diet. Various psychological, nutritional, and microbial factors were identified as predictors of improvement in abdominal pain, constipation, and bloating when following each diet, with notable differences between the two approaches. Study III examined DGBI symptom profiles in individuals with obesity, finding that a significant number of obese individuals experience DGBI symptoms in various GI regions. Comorbid DGBI symptoms in obesity were associated with lower quality of life, increased psychological distress, and non-GI somatic symptoms. While obesity treatment generally reduced the overall prevalence of DGBI, certain specific symptom profiles may actually increase. In Study IV, dietary habits of IBS patients were compared to age- and sex-matched controls from the general population. IBS patients exhibited poorer diet quality compared to controls, and within the patient group, poorer dietary habits were linked to more severe symptoms. Study V identified symptom patterns in patients with DGBI beyond the Rome IV criteria. While confirming the presence of symptom groupings aligned with Rome IV criteria, the study also identified additional patterns that extend beyond anatomical subdivisions. These included an IBS-like factor characterized by meal-related bloating, flatulence, and abdominal pain, and factors encompassing both upper and lower GI symptoms associated with physiological events like meal intake and defecation.

In conclusion, this thesis investigated different aspects of food-related symptoms in patients with a DGBI. Hopefully, this research will contribute to the overall understanding and management of food-related symptoms in DGBI, adding a valuable piece to the puzzle.

SAMENVATTING IN HET NEDERLANDS

Stoornissen van de interactie tussen darmen en hersenen (DGBI) omvatten een reeks aandoeningen die worden gekenmerkt door gastro-intestinale (GI) symptomen, in afwezigheid van alarmerende kenmerken of organische ziekten die de symptomen verklaren, na een minimaal relevant klinisch onderzoek. Eén van de meest voorkomende DGBI is prikkelbare darmsyndroom (PDS), gekenmerkt door buikpijn met veranderd stoelgangspatroon. Veel patiënten met een DGBI voedsel gerelateerde symptomen ervaren, waardoor dieet een prominente positie heeft ingenomen in DGBI onderzoek. Deze thesis heeft als doel om bij te dragen aan het begrijpen van onderliggende mechanismen van voedsel gerelateerde symptomen en het optimaliseren van de diagnose en behandeling van patiënten met DGBI.

Studie I verschafte inzicht in de wereldwijde prevalentie en last van maaltijd gerelateerde buikpijn. Een aanzienlijk deel van de algemene bevolking meldde dit type pijn, dat voornamelijk voorkwam bij vrouwen, jongere individuen, en geassocieerd werd met andere GI- en niet-GI-symptomen, een lagere levenskwaliteit en meer gebruik van gezondheidszorg. Studie II richtte zich op het voorspellen van responsen op het traditionele PDS-dieet en het FODMAP-dieet. Psychologische, voedings- en microbiële factoren werden geïdentificeerd als voorspellers van verbetering van buikpijn, constipatie en opgeblazen gevoel bij het volgen van elk dieet, waarbij opvallende verschillen tussen de twee benaderingen werden waargenomen. Studie III onderzocht DGBI-symptoomprofielen bij individuen met obesitas en onthulde dat een aanzienlijk aantal mensen met obesitas DGBI-symptomen in verschillende GI-regio's ervaart. Het hebben van DGBI-symptomen bij obesitas werd geassocieerd met een lagere levenskwaliteit, verhoogde psychologische stress en niet-GI-somatische symptomen. Hoewel de behandeling van obesitas over het algemeen de algehele prevalentie van DGBI verminderde, kunnen bepaalde specifieke symptoomprofielen juist toenemen. In Studie IV werden de voedingsgewoonten van PDS-patiënten vergeleken met leeftijds- en geslachtsgenoten uit de algemene bevolking. PDS-patiënten vertoonden een lagere kwaliteit van het dieet in vergelijking met de controlegroep, en binnen de patiëntengroep werd een verband gevonden tussen slechtere voedingsgewoonten, zoals verminderde energie-inname en een lagere dieetdiversiteit, en ernstigere symptomen. Studie V identificeerde symptoompatronen bij patiënten met DGBI die verder gaan dan de op de GI anatomie gerichte Rome IV-criteria. Hoewel de aanwezigheid van symptoomgroeperingen volgens de Rome IV-criteria werd bevestigd, werden ook andere patronen geïdentificeerd met een breder symptoomprofiel. Deze omvatten een IBS-achtige factor gekenmerkt door maaltijd gerelateerde opgeblazenheid, winderigheid en buikpijn, en factoren die zowel boven als onder GI-symptomen omvatten die verband houden met fysiologische gebeurtenissen zoals het eten van een maaltijd en ontlasting.

In conclusie onderzocht deze thesis verschillende aspecten van voedsel gerelateerde symptomen bij patiënten met DGBI. Hopelijk levert dit onderzoek een waardevolle bijdrage aan het algemene begrip en de behandeling van voedsel gerelateerde symptomen bij DGBI.

SAMMANFATTNING PÅ SVENSKA

Störningar i interaktionen mellan tarm och hjärna (på engelska disorders of gut brain interaction, DGBI) omfattar ett spektrum av sjukdomstillstånd som kännetecknas av gastrointestinala (GI) symtom i frånvaro av varningssignaler eller organiska sjukdomar som förklarar symtomen efter relevant klinisk utvärdering. En av de vanligaste DGBI är irritable bowel syndrome (IBS), som kännetecknas av buksmärta i kombination med förändrade avföringsvanor. Eftersom många patienter med DGBI rapporterar symtom relaterat till matintag, har kosten fått en central roll inom forskningen vid DGBI. Syftet med denna avhandling är att bidra till en övergripande förståelse för de underliggande mekanismerna vid matrelaterade symtom, för att kunna optimera diagnostisering och behandling av patienter med DGBI.

Studie I gav insikter i den globala förekomsten och bördan av buksmärta relaterat till måltider. En betydande andel av den allmänna befolkningen rapporterade att de upplevde buksmärta i samband med måltider, där de som drabbades frekvent till övervägande del var kvinnor, yngre individer, hade andra GI-symtom och symtom utanför magtarmkanalen, hade sämre livskvalitet och brukade sjukvård oftare. Studie II fokuserade på att prediktera symtomrespons på den traditionella IBS-dieten och en låg FODMAP-diet. Psykologiska, näringsmässiga och mikrobiella faktorer identifierades som prediktorer vid respektive diet till förbättring av buksmärta, förstoppning och uppblåsthet, med påtagliga skillnader mellan de två dieterna. Studie III undersökte DGBI-symtom hos individer med fetma och fann att en betydande andel av personer med fetma upplever DGBI-symtom i olika delar av magtarmkanalen. Samtidig förekomst av DGBI-symtom och fetma var förknippat med sämre livskvalitet, ökad psykologisk stress och symtom utanför GI-kanalen. Trots att behandling av fetma minskade den totala förekomsten av DGBI generellt sågs en ökande förekomst av vissa specifika magtarmsymtom. I Studie IV jämfördes kostvanor hos IBS-patienter med ålders- och könsmatchade kontroller från den allmänna befolkningen. IBS-patienter hade en sämre kostkvalitet jämfört med kontrollerna och inom patientgruppen kunde sämre kostvanor, såsom lägre energiintag och mindre varierat kostintag, kopplas till svårare symtomgrad. Studie V identifierade mönster av symtom som sträckte sig bortom de nuvarande Rome IV-kriterierna hos patienter med DGBI. Samtidigt som studien bekräftade förekomsten av symtomgrupperingar i linje med Rome IV-kriterierna, identifierades även mönster som sträcker sig bortom de nuvarande anatomiska indelningarna. Dessa inkluderade en IBS-liknande faktor som kännetecknas av uppblåsthet, gaser och buksmärta i samband med måltider, samt faktorer som omfattade både övre och nedre magtarmsymtom som var kopplade till måltidsintag och tarmtömning.

Sammanfattningsvis undersökte denna avhandling olika aspekter av matrelaterade symtom hos patienter med DGBI. Förhoppningsvis kommer denna forskning att bidra till den övergripande förståelsen och behandlingen av matrelaterade symtom vid DGBI, och därmed addera en värdefull pusselbit för att optimera omhändertagandet av denna patientgrupp.

LIST OF PAPERS

This thesis is based on the following studies, referred to the text by their Roman numerals.

I. Colomier E, Melchior C, Algera JP, Hreinsson JP, Störsrud S, Törnblom H, Van Oudenhove L, Palsson OS, Bangdiwala SI, Sperber AD, Tack J, Simrén M.
Global prevalence and burden of meal-related abdominal pain
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II. Colomier E, Van Oudenhove L, Tack J, Böhn L, Bennet S, Nybacka S, Störsrud S, Öhman L, Törnblom H, Simrén M.
Predictors of symptom-specific treatment response to dietary interventions in irritable bowel syndrome
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III. Colomier E, Halminen J, Björck M, Höskuldsdóttir G, Mossberg K, Engström M, Eliasson B, Wallenius V, Fändriks L, Tack J, Törnblom H, Simrén M.
Prevalence and factors associated with disorders of gut-brain interaction in obesity before and after treatment
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Habitual dietary intake and diet quality of patients with irritable bowel syndrome vs. the general population
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Symptom patterns outside the Rome IV consensus in both Eastern and Western patients with a disorder of gut-brain interaction
Submitted

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ABBREVIATIONS

DGBI	Disorder(s) of gut-brain interaction
GI	Gastrointestinal
QoL	Quality of life
CNS	Central nervous system
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency
IBS	Irritable bowel syndrome
ENS	Enteric nervous system
IBS-C	Irritable bowel syndrome with predominant constipation
IBS-D	Irritable bowel syndrome with predominant diarrhea
IBS-M	Irritable bowel syndrome with mixed bowel habits
IBS-U	Unsubtyped irritable bowel syndrome
BSF	Bristol Stool Form
PI-IBS	Post-infectious irritable bowel syndrome
SI	Sucrase-isomaltase
FODMAPs	Fermentable oligo-, di-, monosaccharides, and polyols
MRI	Magnetic resonance imaging
EECs	Enteroendocrine cells
GPCRs	G-protein coupled receptors
TRP	Transient receptor potential channels
TRPV1	Transient receptor potential channels vanilloid 1
NICE	National Institute for Health and Care Excellence
FD	Functional dyspepsia
MRGPRX2	Mas-Related G Protein-Coupled Receptor-X2
IgE	Immunoglobulin E
NaCl	Sodium chloride
WHO	World Health Organization
BMI	Body mass index
GERD	Gastroesophageal reflux disease
SG	Sleeve gastrectomy
RYGB	Roux-en-Y gastric bypass
BDA	British dietetic association
ARFID	Avoidant restrictive food intake disorder
CBT	Cognitive behavioral therapy
VLED	Very low energy diet

SCB	Statistics Sweden
EAR4Q	Enhanced Asian Rome IV Questionnaire
GSRS-IBS	Gastrointestinal Symptoms Rating Scale for IBS
PHQ	Patient Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
BAI	Beck Anxiety Inventory
VSI	Visceral Sensitivity Index
EQ-5D	EuroQol Five-Dimensional questionnaire
DQI-SNR	Diet Quality Index for Swedish Nutrition Recommendations
SD	Standard deviation
CI	Confidence intervals
d	Cohen's effect size
η^2	Partial eta squared
EFA	Exploratory factor analysis
CFA	Confirmatory factor analysis
RMSEA	Root mean square error of approximation
F1	Factor 1
EPS	Epigastric pain syndrome

1. INTRODUCTION

1.1. Disorders of gut-brain interaction

Disorders of gut-brain interaction (DGBI), formerly known as functional gastrointestinal disorders, encompass a range of conditions characterized by persistent or recurring gastrointestinal (GI) symptoms (1). Despite their high global prevalence of 40% (2), the underlying causes of DGBI remain largely unknown. Patients with DGBI do not exhibit any identifiable organic, systemic, or metabolic diseases that could account for their symptoms, at least not on the minimally invasive routine clinical measurements.

The definition of DGBI has undergone changes influenced by societal perspectives on illness and disease, scientific evidence, as well as the training and personal biases of clinicians. Throughout history, DGBI have often been viewed as less valid conditions compared to pathologically identified diagnoses, leading to potential stigmatization of patients with a DGBI who do experience real symptoms. This perspective stems from the impact of dualistic principles that categorize "organic" disorders as inherently real, while functional disorders (nonstructural disorders) are frequently considered to be imagined, psychiatric or ill-defined. However, the definition has evolved over time, shifting from an understanding of DGBI as the "absence of organic disease" or stress-related or psychiatric disorders to being recognized as motility disorders or disorders of GI function.

To approach these disorders scientifically and eliminate bias, the Rome Foundation has developed and continually refined meaningful working definitions for DGBI. Composed of experts in the field who have dedicated over two decades to studying these disorders, the foundation recognizes the necessity to identify DGBI patients as accurately as possible to facilitate research in this patient population. During the development of DGBI definitions, the experts employed the Delphi method (3), a collaborative approach that seeks consensus through iterative feedback (not necessarily complete agreement). This technique enables them to address challenging questions that may not be easily tackled through translational methods. Throughout the process, it was deemed essential for the recent DGBI definition to be positive in nature (rather than reliant on exclusionary criteria), reflective of current scientific knowledge, and free from stigmatization. The agreed-upon definition currently used for DGBI is: “a group of disorders classified by GI symptoms related to any combination of:

- Motility disturbances
- Visceral hypersensitivity
- Altered mucosal and immune function
- Altered gut microbiota
- Altered central nervous system (CNS) processing” (1).

1.2. Rome IV diagnostic criteria and classification

Due to the absence of objective and clinically available biomarkers, the Rome Foundation used the same Delphi method to develop diagnostic criteria and a classification system. While the diagnostic Rome IV criteria are increasingly employed in clinical settings, their primary purpose is to support epidemiological and clinical research. Consequently, these criteria have been recommended by regulatory agencies such as the FDA, EMA, and other regulatory agencies as entry criteria for clinical trials, and they continue to be the sole method used to diagnose patients in epidemiological surveys.

In total, there are over 30 DGBI entities, which are classified based on the specific anatomical region of the GI tract presumed that there are unifying features underlying diagnosis and management that relate to these specific GI regions (**Figure 1**) (4). Hence, within the respective anatomical region, the predominant symptom of a DGBI is experienced. The mere localization of symptoms is inadequate to address certain DGBIs, such as irritable bowel syndrome (IBS), which is primarily characterized by pain. This conditions is difficult to pinpoint and is affected by a wider influence caused by a dysregulation of symptom control pathways between the CNS and the enteric nervous system (ENS), which is also a discussion point of study V in this thesis. Moreover, DGBI exhibit shared physiological characteristics as outlined in the DGBI definition (5). However, the relative contribution of these factors can vary based on the location of symptoms, symptom duration, and individual differences among patients or within the same patient over time. For instance, fecal incontinence primarily arises from disturbances in motility, whereas IBS is a more intricate condition involving a combination of factors, including motility disturbances, visceral hypersensitivity, mucosal immune dysregulation, microbiota alterations, and CNS-ENS dysregulation. Hence, while classification systems are vital for categorizing these disorders, effective management requires a biopsychosocial approach that acknowledges the variability and complexity in DGBI.

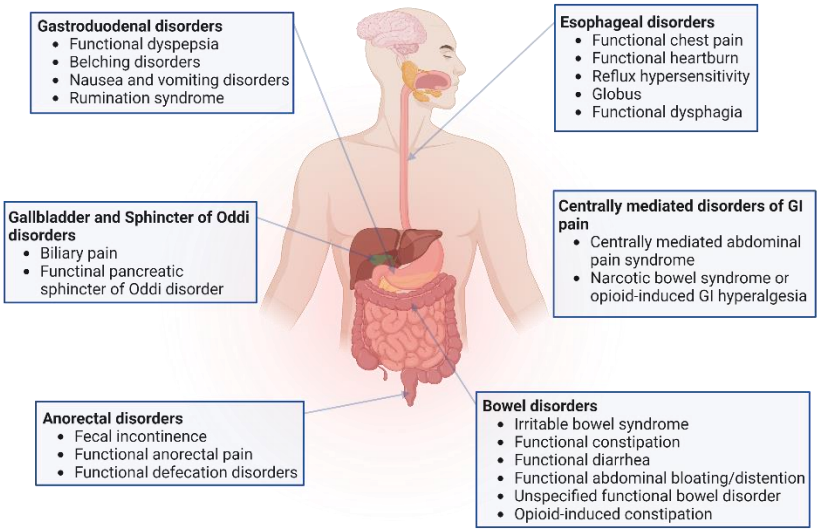

Figure 1. *DGBI entities categorized according to anatomical region in the GI tract.*

1.3. Irritable bowel syndrome

Among the various DGBI, IBS stands out as one of the most widespread worldwide and will be the primary focus of this thesis. Approximately 4% of the global population suffers from IBS (2).

IBS is a complex DGBI, classified under the bowel disorders, that can present itself through a variety of manifestations. The syndrome is characterized by recurrent abdominal pain associated with altered bowel habits (1). IBS, despite being a benign disorder with favorable outcomes in terms of morbidity and mortality, exerts a significant impact on both individual patients and society. This impact is evident through the presence of co-existing non-GI symptoms, (disease-specific) psychological distress, impaired quality of life (QoL), increased healthcare utilization and healthcare costs, and reduced work productivity (6).

IBS is commonly categorized into various subtypes depending on the predominant bowel habit. These subtypes include constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), mixed IBS (IBS-M) characterized by a combination of constipation and diarrhea, and unsubtyped IBS (IBS-U). To aid in the subtyping process, a stool diary based on the Bristol Stool Form (BSF) scale can be used (**Figure 2**) (7).

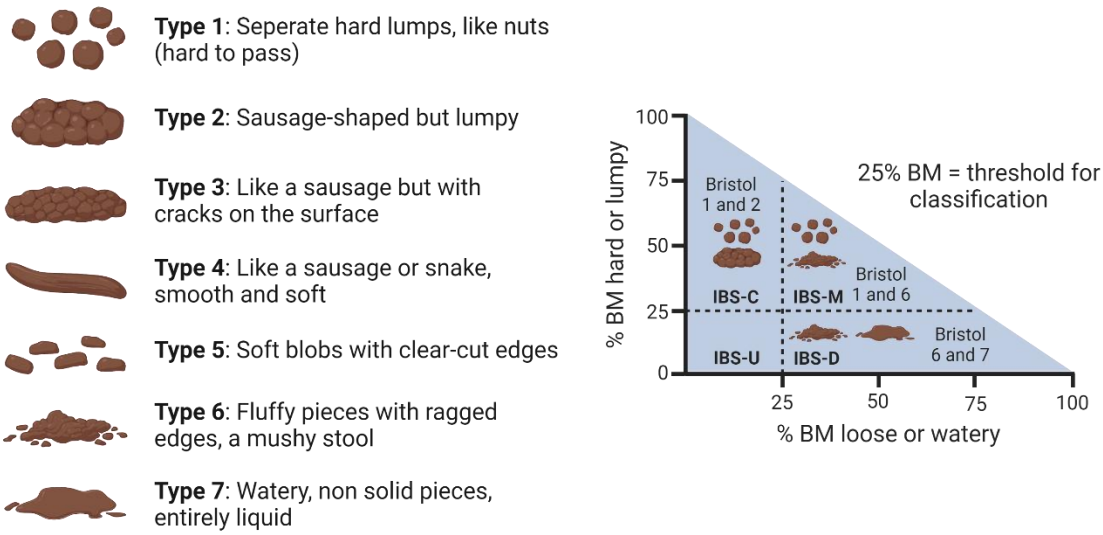

Figure 2. *BSF scale with IBS subtyping graph. (BM: bowel movements)(adapted from Mearin e al. Bowel Disorders. Gastroenterology. 2016 Feb 18;S0016-5085(16)00222-5., reprinted with permission)*

More recently, researchers have proposed the inclusion of comorbidities alongside the predominant bowel habit when subtyping patients to allow the development of a more personalized treatment algorithm. Through the use of multivariate modeling, Polster et al. successfully identified five subgroups of IBS patients; 1) constipation-predominant, 2) diarrhea-pain-predominant, 3) mixed-high psychological symptoms, 4) mixed-moderate psychological symptoms, and 5) overall mild symptoms (8). This method of subtyping holds the potential to offer deeper insights into the underlying pathophysiology of each patient, which can be valuable for patient selection and assessing treatment

outcomes in clinical studies. Black et al. also evaluated this way of subgrouping patients with IBS and were able to find seven similar subgroups characterized by varying degrees of GI symptoms, non-GI symptoms, and psychological comorbidity (9). Additional research is required to determine whether these subgroups can be utilized to guide treatment decisions.

In addition to the aforementioned four subtypes, post-infectious IBS (PI-IBS) is recognized as a distinct subgroup of patients in which the onset of IBS occurs following an episode of gastroenteritis, usually caused by a bacterial infection (10). Studies indicate that the odds of developing IBS following an infectious gastroenteritis is sixfold higher (11). During the infection, patients experience acute IBS-like symptoms, and in 3−36% of cases, these symptoms persist even after the recovery from the gastroenteritis (12). Patients with PI-IBS typically exhibit diarrhea-predominant bowel habits and have a lower incidence of psychological comorbidity.

1.4. Food intolerance as a pathophysiological feature

DGBI arise from a complex set of pathophysiological features and remains only party understood up to date. As the definition describes, the multifactorial pathophysiology is explained by abnormal GI motility (13, 14), visceral hypersensitivity (15), alterations in mucosal and immune function (16, 17), modified communication between the gut and brain (18), altered microbiota (19, 20), genetic predispositions (21), and food intolerances (22, 23). The aspects of food-related symptoms are the focus of this thesis and will therefore be covered more in depth.

A subset of patients with a DGBI report that their symptoms are linked to food intake, emphasizing the significance of dietary factors in the pathophysiology of DGBI, and IBS specifically (22, 24-26). Food-related symptoms are not limited to patients with DGBI; recent findings indicated that 34% of the global population associates abdominal pain with meal intake (study I) (27). Among patients with IBS, the prevalence of food-related symptoms increases to 60−80%. According to the limited publications on trigger foods in IBS, the most common triggers are shown in **Figure 3** (24, 25, 28).

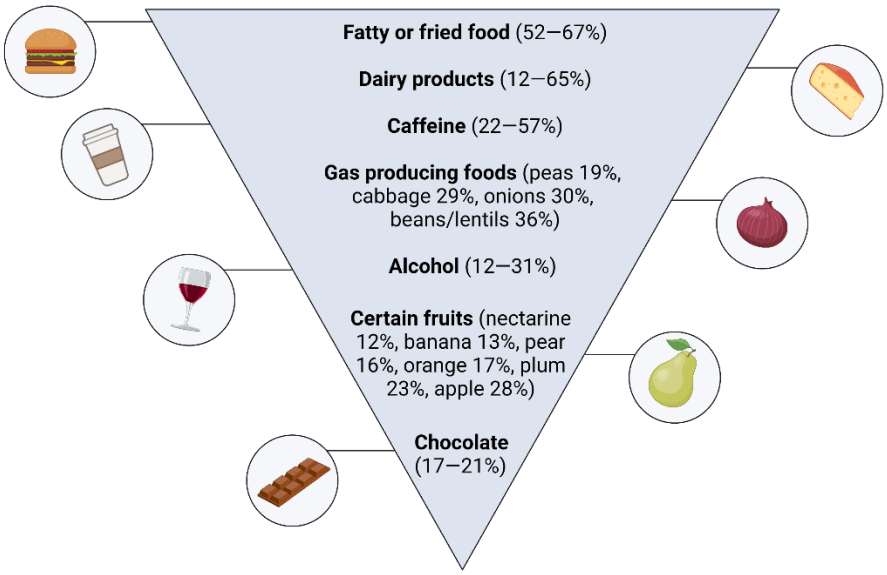

Figure 3. *Trigger foods most frequently reported by patients with IBS.*

Only a restricted number of studies have investigated underlying mechanisms of food intolerances in DGBI. Various concepts are currently being discussed, including physical effects after eating (intestinal content, transit time, colonic motor responses and fermentation), nutrient sensing, malabsorption and intolerances, interactions with microbiota, as well as local allergic and immune reactions (**Figure 4**) (23, 29).

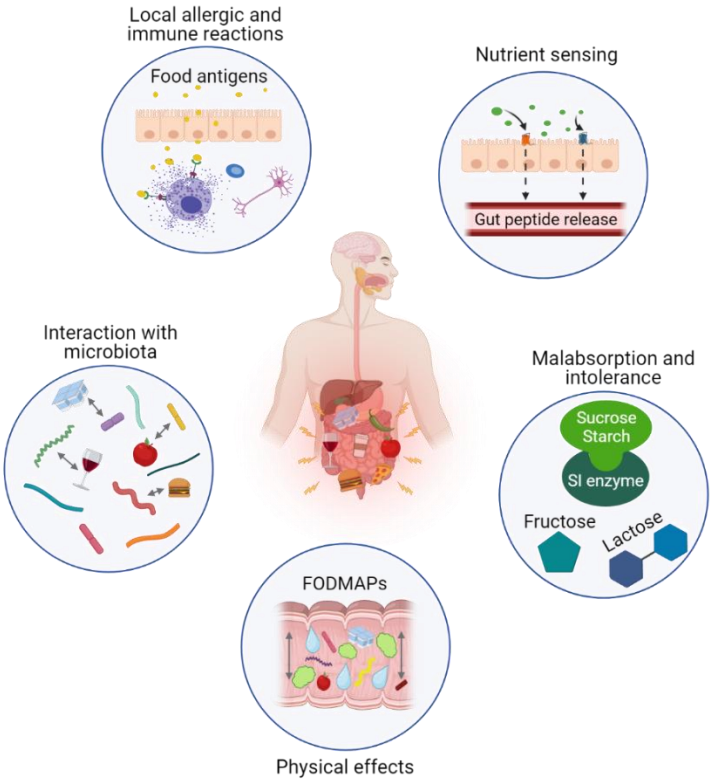

Figure 4. *Underlying mechanisms explaining food-related symptoms in DGBI. from Colomier et al. Mechanisms underlying food-related symptoms in disorders of gut-brain interaction: Course ahead in research and clinical practice. Best Pract Res Clin Gastroenterol. 2023 Feb-Mar;62-63:101824., reprinted with permission)*

1.4.1. Physical effects: intestinal content, motility, and fermentation

Meal volume and caloric load impact intestinal content, and sensory and motor responses throughout the GI tract. These factors are considered important as they can be easily modified through lifestyle changes. The initial approach to managing IBS, known as the traditional IBS diet, focuses on self-management principles such as controlling portion sizes, chewing food thoroughly, avoiding overeating, maintaining regular meal times, and ensuring adequate fluid intake (30, 31). These aspects will be further addressed in detail in the multidisciplinary care section below.

A recent study, investigating features of IBS patients after consuming a lactulose-containing nutrient drink, revealed a reciprocal association between postprandial symptoms, transit time, and hydrogen/methane production (32). Another study comparing levels of gas and fluid in the intestines of patients with a DGBI, specifically those with IBS-D, and healthy controls showed that after the intake of short-chain carbohydrates, the intestinal content is similar. However, patients with a DGBI can experience symptoms presumably due to visceral hypersensitivity, i.e., a decreased perception threshold for visceral stimuli or increased perceived intensity of visceral sensations, and changes in gut-brain interactions (15, 33, 34). Furthermore, MRI studies have reported that IBS-D patients may have lower small bowel water content compared to healthy individuals (35, 36). These MRI findings also demonstrated that the transit time after consuming food is faster in IBS-D patients than in controls.

Older studies with limited sample sizes indicated that IBS patients exhibit increased colonic motor activity and higher pressure wave amplitudes compared to controls (37, 38). Patients also experienced prolonged elevation of colonic motor activity after meals, including more high amplitude propagating contractions and rapid colon transit potentially due to disrupted gut peptide release and ENS function (39, 40). The altered colonic response, such as increased cholecystokinine release, may explain symptom onset after consuming fatty foods, which stimulate colonic motor activity (24, 41-43). Studies have shown that duodenal lipid infusion increases rectosigmoid pressure, induces colonic hypersensitivity, and delays colonic transit. Additionally, gas transit can be disturbed due to gas retention in IBS patients after duodenal lipid infusion (44-46). These findings highlight the importance of changes in dysregulated motility (i.e., transit time and colonic motor activity) and emphasize the role of sensory alterations and gas production in the pathophysiology of DGBI (47, 48).

1.4.2. Nutrient sensing

Chemosensing receptors, mechanoreceptors, and thermoreceptors across the mucosa of the GI tract detect nutrients and send signals to the brain through neural pathways and gut peptide release (49-51). Enteroendocrine cells (EECs) express chemosensing G-protein coupled receptors (GPCRs) that release gut peptides and hormones in response to fatty acids, glucose, and amino acids, which affects gastric function (52). Research has shown that food components, such as short chain fatty acids, have the ability

to impact the expression of GPCRs, which in turn can disrupt the function of EECs and their sensitivity to nutrients, potentially leading to visceral hypersensitivity (53).

A second set of receptors expressed by ECCs that can regulate gut peptide release are the transient receptor potential channels (TRP), including TRP vanilloid 1 (TRPV1). The expression of TRPV1 has been linked to increased rectal sensitivity in patients with IBS following duodenal lipid infusion (54). Moreover, TRPV1 receptors can be activated by capsaicin, suggesting a potential involvement in thermosensitivity. Studies have demonstrated that individuals with DGBI exhibit hypersensitivity to capsaicin administration, indicating a possible increase in TRPV1-immunoreactive nerve fibers or heightened reactivity to TRPV1 receptor activation (55, 56). Consequently, additional research into the chemosensitivity and thermosensitivity to nutrients in patients with a DGBI may be warranted, as these factors could potentially contribute to the manifestation of symptoms.

1.4.3. Malabsorption

While there is no evidence suggesting a higher prevalence of malabsorption syndromes in patients with DGBI compared to the general population, it is possible that malabsorption of specific food components contributes to food-related symptoms more frequently in DGBI (57-60). The first aspect to consider is lactose malabsorption, which refers to the inability to digest lactose due to the downregulation of lactase, the enzyme responsible for breaking down lactose in the small intestine. When lactose malabsorption results in IBS-like symptoms following lactose consumption, it is referred to as lactose intolerance which might be more common in patients with IBS compared to healthy controls. Visceral hypersensitivity and colonic fermentation leading to gas production are both suggested to be involved in the development of lactose intolerance. Hydrogen breath testing or empirical lactose elimination for two weeks are used for the diagnosis. However, a lactose-free diet in DGBI, and IBS in particular, lacks sufficient evidence for a widespread recommendation (30, 61). Similarly, malabsorption of fructose, poorly absorbed when in excess to glucose, may cause symptoms in susceptible individuals as a consequence of fermentation by the gut microbiota leading to gas production (33, 62, 63). However, studies assessing a fructose-free or low-fructose diet in patients with a DGBI are limited and inconclusive (64-66).

More recent literature has shown that the prevalence of a defective sucrase-isomaltase (SI) gene is increased in IBS patients, particularly IBS-D, leading to sucrose intolerance (67, 68). SI deficiency, which can be inherited or acquired, results in osmotic diarrhea and gas production due to presence of unabsorbed carbohydrates (69, 70). Reduced SI activity may impede response to the traditional IBS diet according to the recommendations of the National Institute for Health and Care Excellence (NICE) or a diet restrictive of fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs) (71). The limited efficacy may be attributed to the fact that these diets do not fully address the consumption of sucrose and only partially reduce starch intake. Limited studies suggest benefits of a low-sucrose and starch diet

in improving both GI and non-GI symptoms in IBS (72, 73). While malabsorption syndromes occur similarly in DGBI patients and the general population, sensitivity to malabsorbed carbohydrates appears exaggerated in DGBI. Food intolerances are common, but there is insufficient evidence to recommend exclusion diets for all DGBI patients

1.4.4. Food-microbiota interaction

Gut microbiota are believed to play a crucial role in the development of food-related symptoms in DGBI. Research suggests that IBS is associated with reduced gut microbial diversity compared to healthy individuals. Distinct symptom-related and subtype-specific compositional and functional differences in both the microbiome and metabolome have been observed between patients with IBS, and controls (74-78).

Emerging research has shown that food components, such as FODMAPs and tryptophan interact with the gut microbiota, which can trigger the release of neuroactive mediators, such as histamine, lipopolysaccharides and proteases (79-83). These mediators may modulate intestinal nociceptive signaling and potentially amplify visceral hypersensitivity (79, 80). Ex vivo mice experiments showed that perfusing fecal supernatants of IBS patients in the colon of mice could cause hypersensitivity in visceral nerves, an effect blocked by protease inhibitors, histamine antagonists, and a low-FODMAP diet (81).

Another research topic and treatment supporting the role of the food-microbiota interaction is fecal microbiota transplantation.

Dietary treatments employed in DGBI have demonstrated both positive and negative alterations in microbiota and metabolite profiles (61, 84-90). Specifically, a low FODMAP diet has been shown to reduce the presence of beneficial bacteria, including Bifidobacteria, in DGBI patients (86). Additionally, the composition of the gut microbiota and metabolite profiles prior to dietary interventions have proven to be predictive of the response to dietary therapy (study II) (88, 91, 92). Furthermore, another microbiota-altering intervention, fecal microbiota transplantation, has been described as a promising treatment option for patients with IBS. By transferring healthy gut bacteria from a donor to a recipient, fecal microbiota transplantation can restore the balance of the gut microbiome, potentially alleviating food-related symptoms in IBS (93, 94). This innovative approach holds great potential. However, further studies are warranted before any clear conclusions can be drawn regarding gut microbiota profiles and the effect of FMT on DGBI symptoms. Overall, the diet-microbiota interaction in DGBI patients involves factors such as microbial composition, function, and metabolites. These elements collectively contribute to both the generation of symptoms in DGBI and the management of those symptoms. Future larger scale research should aim to validate these findings to further finetune appropriate treatment choices.

1.4.5. Local allergy-like reaction to food

Systemic IgE-mediated food allergies are rare in DGBI patients, making them an unlikely cause of food-induced symptoms (95). However, recently emerging evidence shows that a subgroup of IBS patients present with a local allergy-like reaction in the duodenum, i.e., a localized rapid mucosal permeabilization response, after exposure to food components (96, 97). Patients who showed no classical allergic sensitization using serum samples underwent confocal laser endomicroscopy to observe the intestinal epithelium in real-time. By administering intravenous fluorescein and using low-energy blue laser illumination, researchers were able to observe acute alterations in the duodenal mucosa after food solution administration in more than half of the IBS patients. Baseline alterations included increased intraepithelial lymphocytes, breaks between epithelial cells, and enlarged intervillous spaces. Exposure of food proteins led to extravasation of fluorescein and cell shedding into the duodenal lumen. Patients with functional dyspepsia (FD) have shown comparable changes in mucosal integrity, with a higher epithelial gap density in the duodenum compared to healthy individuals (98). Altered enteric neural function in FD may be linked to low-grade inflammation, elevated mast cell and eosinophil counts, and increased mucosal permeability in the duodenum, potentially influenced by food reactivity (99, 100).

The Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) presents another potential explanation for this local immune response. MRGPRX2 is a flexible receptor that can be triggered by diverse ligands such as eosinophilic cationic peptide, substance P, beta-defensins, major basic protein, opioids, quorum sensing molecules from gram-positive bacteria, and quinolone antibiotics. Recent research has confirmed MRGPRX2's presence in mast cells of the gastrointestinal tract, implying its role in inflammatory conditions (101, 102).

Food reactivity in DGBI can also contribute to the development of visceral hypersensitivity. A study showed that the presence of food antigens during an acute bacterial GI infection induced a localized immune response to food in the colon of mice (103). After recovering from the infection, exposure to the specific food antigen caused colonic mast cells to undergo IgE-dependent degranulation, releasing histamine, leading to visceral nociceptor sensitization and increased perception of visceral pain, i.e. visceral hypersensitivity. Importantly, hypersensitivity was only observed when the food protein was present during the previous infection and seemed to be specific to the antigen. The colon of these mice exhibited elevated levels of protein-specific IgE antibodies, but these antibodies remained undetectable in the serum. Additionally, activation of histamine receptor H_1 potentiated the function of TRPV1 ion channels in dorsal root ganglion neurons, further contributing to the development of visceral hypersensitivity. In IBS, researchers observed that mucosal mast cells carrying surface-bound IgE were situated closer to nerve endings compared to healthy controls, indicating a potential mast cell-neuron interaction in IBS (104). To investigate whether food antigens can trigger a local colonic immune response in controls and patients with IBS, they utilized the colonoscopic allergen provocation test (103,

105). During this test, dietary antigens (wheat, soy, milk, and gluten) as well as a negative (0.9% NaCl) and positive (histamine) control solutions were injected into the mucosa of the colon. The onset of sufficient mucosal edema following injection was assessed by analyzing images and video-recordings of the sites of injection before and after the procedure. Interestingly, all IBS patients exhibited mucosal reactions to at least one dietary antigen, while only a few controls did. These findings suggest that food antigens may activate mast cells in patients with IBS, potentially involving a local IgE-mediated mechanism.

Limited studies have also explored the relationship FODMAPs and local immune responses in DGBI. The low FODMAP diet, known for its efficacy in improving IBS symptoms, has been associated with improved mucosal integrity and decreased urinary histamine levels in IBS patients (106). All these findings highlight the existence of local immune reactions to food in a subset of patients with a DGBI and emphasize the need to further study this pathophysiological aspect.

1.5. Link between obesity and disorders of gut-brain interaction

As study III in this thesis focuses on the prevalence and burden of DGBI in individuals with obesity, it was decided to dedicate a paragraph in the introduction to the association between obesity and DGBI. Latest WHO reports indicate that 11% of the male and 15% of the female global population are living with obesity (107). Obesity is characterized by the abnormal or excessive accumulation of fat, which can have detrimental effects on health. The condition is typically defined by a body mass index (BMI) of 30 kg/m^2 or higher. However, it is important to note that BMI alone may not accurately reflect fat proportions in different individuals, and should be used as a general indicator. In individuals with obesity, the high BMI is a result of an imbalance between calorie intake and expenditure, influenced by environmental, genetic, and behavioral factors. Risk factors for the development of obesity include a sedentary lifestyle, low socioeconomic status, and increasing age (108).

Previous research has identified an association between obesity and GI symptoms. A meta-analysis has highlighted that increasing BMI is associated with various GI symptoms such as abdominal pain, gastroesophageal reflux, vomiting, chest pain or heartburn, retching, and incomplete rectal evacuation (109). Among the DGBI in general, and IBS in particular, there have been inconsistent findings about the association between IBS and obesity or increasing BMI (110-112). On the other hand, the link between obesity and gastroesophageal reflux disease (GERD) appears to be well-established. Most epidemiological data supports an association between higher BMI and GERD symptoms, with adiposity likely playing a role in this relationship (113). However, the prevalence of other DGBI in individuals with obesity remains understudied.

Furthermore, limited research has been conducted on the impact of obesity treatment on the presence of comorbid GI symptoms. It has been shown that a surgical procedure, the sleeve gastrectomy (SG) may lead to increased severity of post-operative GERD symptoms, while Roux-en-Y gastric bypass (RYGB)

has been associated with more severe abdominal pain scores (114, 115). However, more comprehensive studies are needed to fully understand the burden of DGBI in obesity and the effects of obesity treatment on this burden.

1.6. Multidisciplinary care approach with a focus on IBS

DGBI are heterogeneous conditions characterized by a wide array of symptoms and varying patient profiles. Treating DGBI, or IBS, according to a 'one size fits all' approach is a mistake. There are numerous pharmacological and non-pharmacological treatments, including dietary interventions, but their effectiveness is limited to specific subgroups of patients.

Promoting a multidisciplinary care model entails giving equal importance to patient education, pharmacotherapy, lifestyle and dietary modifications, as well as psychotherapy or behavioral interventions. These treatment strategies should be discussed with the relevant healthcare professionals, including gastroenterologists, certified dieticians, psychiatrists, and psychologists (**Figure 5**). Setting realistic stepwise goals and having a good patient-physician relationship in which the patient feels heard and part of the decision-making process can only be beneficial for the outcome (116, 117).

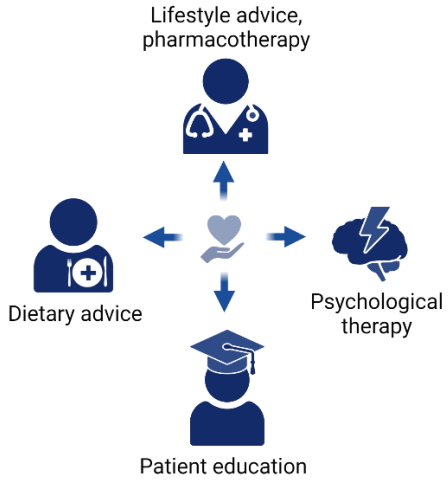

Figure 5. *Multidisciplinary care approach in IBS management.*

Since food-related symptoms and diet in IBS are the main focus of this thesis, pharmacological, psychological and behavioral therapy will only be discussed briefly and the traditional IBS and low FODMAP diet will receive more attention.

1.6.1 Pharmacological treatment for IBS

Medicinal products, including products without traditional active agents (such as probiotics) are selected according to the predominant symptom (**Figure 6**), focusing on managing the symptom itself rather than addressing their root cause (118, 119). In some cases, a combination of medicines may be required to achieve optimal effectiveness. For patients experiencing severe and persistent symptoms, a combination of psychotropic medications, referred to as centrally acting neuromodulators, and other treatment modalities, such as behavioral or psychological therapy, can be advised.

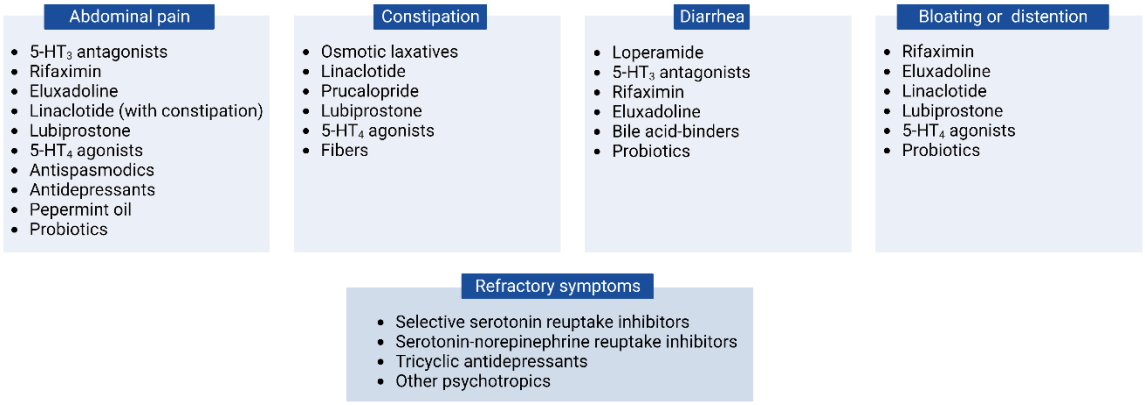

Figure 6. *Pharmacological treatment options in IBS.*

1.6.2. Lifestyle and dietary advice in IBS

1.6.2.1. Traditional IBS dietary/lifestyle advice

The traditional dietary and lifestyle advice for IBS, proven to be effective in 40−50% of the patients, is based on the NICE and the British dietetic association (BDA) guidelines with its primary use in primary care and its focus on the importance of self-management principles (30, 31).

Patients are advised to have regular meals, take time to properly chew meals, avoid skipping meals, never feel too full, and maintain a sufficient amount of fluid intake, especially water and non-caffeinated drinks (at least 8 cups per day). The BDA recommendations also state that although the evidence for the use of probiotics is limited, it is generally considered safe to try them as a potential management option. In general, the patients should be recommended a healthy balanced diet with a regular eating pattern.

Even though the guidelines are more focused on “how” and “when” to eat instead of “what” to eat, they do also recommend to limit the intake a handful of potential triggers;

- For patients who associate their symptoms with caffeine intake, it is advised to restrict coffee and tea consumption to a maximum of three cups per day.
- Alcohol intake, including fizzy drinks, should be monitored and kept within safe national limits, with screening for binge drinking.
- High-fiber foods, particularly bran and whole grains, should be consumed in moderation, and resistant starch should be avoided. Patients experiencing constipation and bloating may find relief by incorporating oats and linseeds (1−2 tablespoons per day) into their diet.
- If there is suspicion of milk sensitivity or a positive lactose hydrogen breath test, a low lactose diet can be considered.
- Fat intake should be assessed and adjusted to align with national healthy eating guidelines if patients associate it with symptoms.
- Similarly, if spicy foods are linked to symptoms, it may be beneficial to restrict the consumption.
- Fruit intake should be limited to three servings per day.

- Patients with diarrhea should avoid the artificial sweetener sorbitol.
- While no specific recommendations regarding gluten intake can be made, there is insufficient evidence to support its restriction.

1.6.2.2. The low FODMAP diet

When the initial dietary strategies recommended in traditional IBS guidelines do not provide sufficient symptom relief, a low FODMAP diet is often suggested. The dietary recommendation of restricting FODMAP intake, known as the low FODMAP diet, is specifically designed for managing patients with IBS and has demonstrated effectiveness in controlled studies (120). FODMAP is a term used to describe a group of short-chain carbohydrates that are not fully absorbed in the small intestine. This group includes excess fructose (fructose in excess of glucose), lactose, galacto-oligosaccharides, fructans or fructo-oligosaccharides, and polyols (sorbitol and mannitol) (121). These carbohydrates reach the colon, undergo fermentation, which leads to gas production in the colon. They are also osmotically active, increasing water content in the lumen (122). These mechanisms can cause distention of the intestines, resulting in symptoms such as abdominal pain, diarrhea, flatulence, and bloating in susceptible individuals (62). However, FODMAP ingestion typically does not cause GI symptoms in healthy adults. Research found that the reason why patients with IBS, but not healthy individuals experience symptoms after FODMAP intake could be the presence of visceral hypersensitivity and underlying abnormalities in gut physiology or alterations in gut microbiota activity and composition (123).

The diet starts with a FODMAP elimination phase, which is typically followed for two to six weeks (121). Patients then systematically reintroduce high-FODMAP foods (6−10 weeks) to identify specific trigger foods (124). Finally, a personalization phase follows, which typically spans up to six months. During this phase, the objective is to reintroduce as many FODMAPs as possible into the diet to enhance food variety and ensure that diet does not restrict one's ability to live their life fully. Various studies have shown the benefits of a low FODMAP diet compared to other or ‘habitual’ diets with a number needed to treat of 5 (125). However, the clinical trials assessing the effects of low FODMAP interventions in patients with IBS have focused on the elimination phase alone. Only limited studies and ongoing research have shown that with reintroduction and a longer follow-up phase, IBS symptom reduction is sustained (126, 127). In addition, studies varied in their designs and control groups, which should be considered when evaluating the true clinical efficacy of the diet. Although a recent meta-analysis suggests low-quality evidence, the low FODMAP diet remains the most supported dietary intervention for reducing IBS symptoms(125).

When applying the low FODMAP diet, one should be aware that the diet is complex, patients need personalized guidance and follow-up from an experienced dietician, and the diet may lead to reduced calorie intake. While dietary interventions are usually considered to be safe, a short-term low FODMAP diet can reduce beneficial gut bacteria and alter the colonic microbiome (88). To potentially counteract

this effect, combining the low FODMAP diet with probiotic supplementation has been shown to safeguard beneficial species in the gut (128). The long-term impact of less restrictive FODMAP diets on the microbiome, as opposed to strict elimination diets, remains uncertain.

Another culprit to consider when discussing trigger foods and demanding exclusion diets, such as the low FODMAP diet, is the nutritional implications of the diet. Exclusion diets can compromise nutrition and calorie intake. Foods rich in FODMAPs are often nutrient-dense, including a diverse range of fruits and vegetables, and breads that provide dietary fiber, prebiotics, vitamins, minerals, and antioxidants. If these foods are not adequately replaced by other nourishing options, this might lead to nutritional inadequacies and a lower-quality diet. Nevertheless, existing literature on the impact of short- and long-term (modified) low FODMAP interventions on diet quality and nutrient intake yields conflicting results. While some studies report an adequate nutritional outcome (129), others indicate a deterioration in nutrient values (130). Therefore, caution is necessary when interpreting these findings. Similarly, when examining the dietary habits of patients with IBS who are not adhering to prescribed intervention diets, it is important to consider that they may have independently modified their habitual diet without seeking guidance from qualified dieticians. In this case, it is also crucial to thoroughly assess the habitual diet quality and nutritional adequacy to avoid diet quality impairment ant malnutrition (study IV).

Lastly, exclusion diets can increase the risk of developing a detrimental fear of food and, consequently, potentially contribute to the development of eating disorders, especially avoidant restrictive food intake disorder (ARFID). Studies indicated that the prevalence of ARFID in DGBI cohorts roughly ranges between 30 and 50% and that this subset of patients has more severe psychological distress and somatic symptoms, and is more likely to have other medical conditions (131).

Similar to drug therapies, opting for dietary interventions should be done mindfully and is only considered effective in a subset of patients. Therefore, it is extremely important to understand for which patients the restrictive low FODMAP diet is the best approach. Research has shown that patients with IBS who are at risk of developing eating disorders tend to adhere more strictly to the elimination phase of the low FODMAP diet compared to those not at risk of eating disorders (132). In addition, literature indicates that around 30% of the patients on the low FODMAP diet apply a prolonged elimination phase, have a reduced caloric intake and the patients also start avoiding non-FODMAP foods (133). Taken together, this could have implications for weight loss, poorer QoL, including the ability to eat socially, and poorer nutrition. These outcomes can, in turn, contribute to the symptoms of IBS (130, 134). For instance, weight loss can lead to changes in motility, persistent fear surrounding food can exacerbate visceral hypersensitivity, and malnutrition can have adverse effects on the microbiota. **Figure 7** illustrates patients who may and may not be suitable candidates for the low FODMAP diet and emphasizes certain aspects that healthcare providers should be mindful of when prescribing the diet (135, 136). Patients who face challenges in accessing food, experience weight loss or failure to gain

weight, or rely on (par)enteral feeding or nutritional supplements should not be considered for the diet. Similarly, patients who already engage in significant dietary restrictions, have a history of exclusion diets, or currently have an active eating disorder are not suitable candidates as they are at risk of developing or worsening their eating disorder. Patients with severe GI-specific anxiety and more negative perceptions of their illness have shown poorer response to the low FODMAP diet and should also be excluded from consideration (study II). Instead, these patients may benefit more from alternatives such as following the traditional IBS guidelines or adopting a "gentle" low FODMAP diet that focuses on reducing the intake of the most prominent trigger food groups rather than complete elimination (137, 138). Furthermore, these patients may be the ones who could potentially benefit from behavioral or psychological interventions.

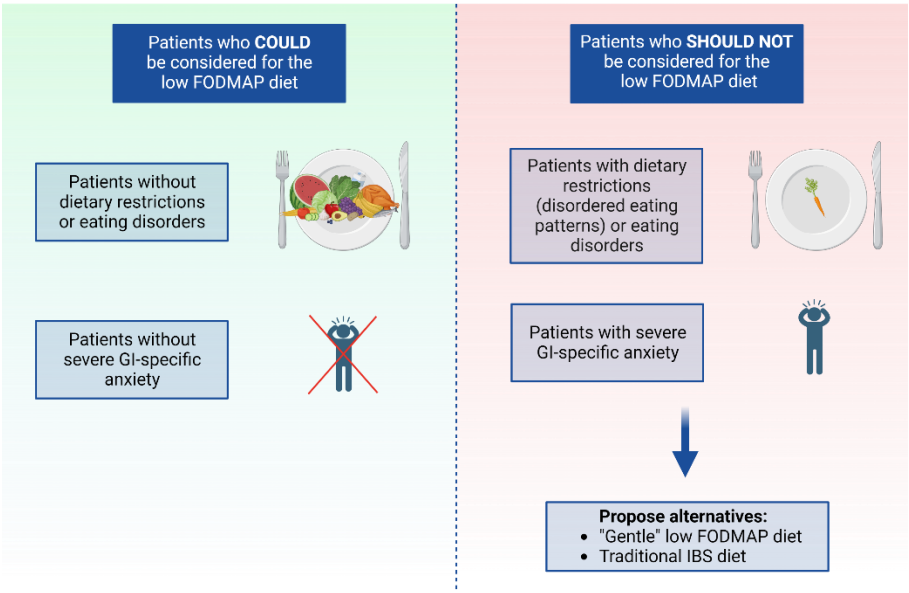

Figure 7. *Appropriate patient selection for the prescription of the low FODMAP diet.*

1.6.2. Behavioral or psychological treatment for IBS

In short, a meta-analysis examining the effectiveness of behavioral and psychological therapies for IBS revealed that self-administered or minimal contact cognitive behavioral therapy (CBT), face-to-face CBT, and gut-directed hypnotherapy were the most extensively studied and found to be effective, with no significant differences among them (139). In the subset of patients who were unresponsive to conventional treatments, group CBT, telephone-based CBT, contingency management, internet-based CBT, dynamic psychotherapy, and gut-directed hypnotherapy were found to be superior to routine care. However, the risks of bias in the included trials was high and the findings should therefore be interpreted with caution. Further exploration in these management options for DGBI is imperative and will be required to assist patients who have depleted all conventional treatment possibilities.

2. AIMS

The general aim of this PhD project is to characterize DGBI patients who self-report food-related GI symptom pattern(s), to enhance our knowledge about underlying mechanisms of food-related symptom and to optimize personalized dietary therapy. The specific aims were to:

I. Describe the global prevalence of meal-related abdominal pain and characterize individuals who frequently experience meal-related abdominal pain with regard to which DGBI diagnoses they fulfill, their GI, non-GI, and psychological symptom pattern, healthcare use, and their quality of life (QoL).

II. Investigate predictors of treatment response to a diet eliminating fermentable oligo-, di-, monosaccharides and polyols and the traditional IBS diet in patients with IBS while focusing on four core IBS symptoms, i.e. abdominal pain, bloating, constipation and diarrhea.

III. Identify the prevalence of GI symptoms compatible with one or more of the specified DGBI in obese patients, characterize this subgroup of patients based on their demographic factors, psychological distress, metabolic function, and QoL, and study the effect of obesity treatment on the prevalence of DGBI.

IV. Assess the habitual dietary intake and diet quality (using a diet quality index) of patients with IBS and subjects representing the general Swedish population. Within the IBS population, we aimed to examine whether dietary habit factors can be associated with specific symptom patterns.

V. Identify specific symptom patterns that potentially involve multiple anatomical regions in contrast to the currently used Rome IV consensus in both Western and Eastern patients diagnosed with a DGBI.

Table 1. *Methodology overview of the five studies*

	Study I	Study II	Study III	Study IV	Study V
Total number	N=54,127	N=67	N=1,121	N=1,292	N=927
Study population	Global general population	IBS	Individuals with obesity	IBS (N=646) and Swedish general population (N=646)	DGBI
Diagnostic criteria	–	Rome III	BMI ≥35 kg/m²	Rome III and IV	Physician diagnosed
Design	Epidemiological	Clinical, interventional	Clinical, interventional	Clinical and epidemiological, non-interventional	Epidemiological
Recruit-ment	Global market survey company, Qualtrics	Secondary/ tertiary care Sweden	Secondary/ tertiary care Sweden	Secondary/ tertiary care Sweden and Statistics Sweden	Secondary/ tertiary care globally
Inclusion period	2019–2020	2013–2014	2015–2017	2010–2022	2020–2023
Primary outcomes	Prevalence and characteristics of meal-related abdominal pain	Predictors of symptom-specific treatment response to low FODMAP and NICE	Prevalence and characteristics of DGBI in obesity	Dietary intake and diet quality of IBS compared to general population	DGBI symptom clusters
Data analyses	Mixed ordinal regression, mixed linear regression	Mixed linear regression	Comparisons, linear contrast analysis,	Standardized mean differences, comparisons, linear regression, ordinal regression	Factor analysis

3. METHODS

3.1. Data sources

3.1.1 Study I

Table 1 gives an overview of all the study cohorts used in this thesis. The participants of study I were anonymously recruited for an online survey study, the Rome Foundation global epidemiology study (2). The epidemiology study was conducted to assess the global prevalence of DGBI using the diagnostic Rome IV criteria. In this study, 33 countries participated, with each country including around 2,000 individuals (**Figure 8**). All the participants completed a survey including the Rome IV questionnaire either during home interviews or online. Once the originally intended results were published, the Rome Foundation granted access to the data upon receiving a relevant research question that aligns with the dataset, which was done for study I of this thesis. Due to differences in methodology, it was recommended not to pool data from both the household and the internet surveys. As a result, we opted to exclusively use the internet data; a nationally representative general population sample of 26 countries (Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Egypt, France, Germany, The Netherlands, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Singapore, South Africa, South Korea, Spain, Sweden, Turkey, UK, and the USA). The Rome Foundation commissioned the global market survey company, Qualtrics (Provo, UT, USA) to collect the sample. Considering the estimated prevalence of the major DGBI being around 5−10% (at the given time), a sample size of approximately 2,000 individuals per country was determined to be sufficient for the originally intended analyses (total n = 54,127). To ensure a balanced representation across countries, prespecified quota-based sampling was employed. This method aimed at including equal proportions of sex (50% female, 50% male), and different proportions in age groups (40% aged 18−39, 40% aged 40−64, and 20% aged 65 years and older) in each country. Prior to engaging in the survey, all participants were obliged to provide electronic consent to enroll in the study, which was presented as a comprehensive "general" health survey to avoid selection bias. Qualtrics provided participant points as rewards that could be redeemed for gifts. To ensure high-quality data, two attention-check questions, a completion-speed check, and repetition questions to identify inconsistent responders were included in the study survey. The software employed automated skip patterns and required responses to all mandatory questions, guaranteeing the absence of missing data.

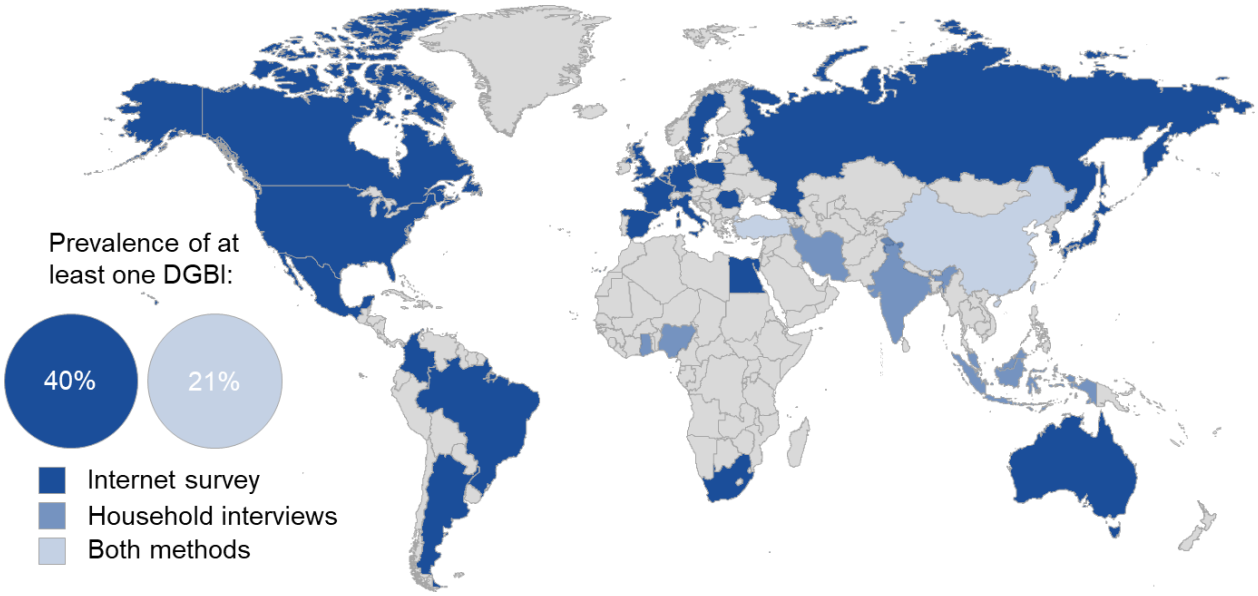

Figure 8. *Rome Foundation global epidemiology study*

3.1.2 Study II

The study population of study II included patients with IBS (n=67, Rome III) who were recruited at the Gastroenterology Outpatient Clinic in Gothenburg and Stockholm, Sweden (secondary/tertiary care centers), for a multi-center, parallel, randomized, controlled, single-blind, comparative trial testing the low FODMAP and the traditional IBS diet (129). Recruiting centers were the gastroenterology outpatient clinics of Sahlgrenska University Hospital, Gothenburg; Karolinska University Hospital, Stockholm; and Sabbatsbergs Hospital, Stockholm (NCT02107625). All participants were adult patients with IBS according to the Rome III criteria, recruited via advertisement in local newspapers. Participants were excluded from the study if they had severe cardiac, liver, neurologic, or psychiatric diseases, or organic GI conditions other than IBS (such as inflammatory bowel disease or celiac disease) that could account for their current symptoms. Additionally, patients following highly restrictive diets that excessively limited certain nutrients (such as low-FODMAP, gluten-free, or vegan diets) were not eligible to participate. However, patients who adhered to a lactose-reduced diet were allowed to join the study, provided they agreed to maintain consistent lactose intake throughout the study period unless advised otherwise (e.g., if assigned to the low-FODMAP diet). Participants were also required to be open to modifying their current dietary habits as part of the study. The use of probiotic products was permitted, but participants were instructed to continue their intake without alteration during the study period. Participants taking IBS medications, including antidepressants, were allowed to participate if they had been using them regularly and at a stable dose for a minimum of one month prior to enrollment.

The study involved three visits, with the initial screening visit focusing on providing participants with written and verbal details about comparing two diets that may relieve IBS symptoms, without disclosing specific diet composition information. Participants were required to complete a 10-day stool diary and a 4-day food diary before the next visit. At visit 2, IBS symptom severity was assessed, and those with

moderate to severe symptoms were eligible for randomization. Eligibility criteria, including dietary habits, were reviewed, and a computer-generated program assigned each patient to either diet A (low-FODMAP) or diet B (NICE) for four weeks. Participants were exclusively informed about either diet A or diet B without any knowledge of the alternative diet, and the term FODMAPs was not mentioned. Three dietitians provided verbal instructions and written materials to participants, offering detailed guidance on which food items to avoid or reduce, as well as suggesting suitable alternatives. To ensure consistency among the dietitians, a one-day meeting was conducted before the study commenced, during which they aligned on the content of the verbal instructions and written materials provided during the randomization visit. Baseline questionnaires were completed, and patients received booklets for tracking their symptoms and diet during the intervention period. At visit 3, the end of the treatment period, completed questionnaires and food diaries were collected. Patients completed a final IBS symptom severity measurement, and compliance with the dietary advice was assessed, along with discussion about potential adverse events during the intervention period.

3.1.3. Study III

The cohort of study III comprised of patients with obesity (BMI≥35 kg/m², n=1,121) who were recruited for a prospective non-randomized cohort study, the BAriatic surgery SUbstitution and Nutrition (BASUN) study, referred for obesity treatment (medical/surgery) in Region Västra Götaland, Sweden (NCT03152617) (140). The patients were managed according to clinical practice guidelines. Follow-up was planned at two, five, and ten years after treatment. Study III only used data of the baseline and follow-up assessments. Patients received either medical or surgical treatment based on the international obesity guidelines, i.e., for surgery, patients needed to have a BMI≥40 kg/m² or 35 kg/m² with comorbidities, such as type 2 diabetes or sleep-apnea (141, 142). Active substance abuse, unstable psychiatric disorders, malignant disease in the last five years, age<18 years or poor general health were strict contraindications and age>60 years a relative contraindication for surgical treatment. Surgical options included Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), the only primary surgical procedures performed in the Swedish public healthcare. Consensus between the patient's preferences, medical condition, and the advice from the operating surgeon determined the final choice of surgical method. Patients with a BMI>30 kg/m² who did not qualify or were not interested in surgery received a one-year medical intervention. Binge eating, severe psychological disturbance or medical conditions were contraindication for the medical treatment.

Laparoscopic antecolic antegastric RYGB was carried out as previously described (143, 144) and SG was performed in line with the state-of-the-art principles described in the Fifth International Consensus Conference on SG (145). Postoperative follow-up at six weeks, six and twelve months were performed in accordance with the Nordic guidelines for follow-up and dietary supplementation after bariatric surgery after which the patients were referred to personal primary healthcare units for continued yearly follow-up. Dietary supplementation included 100 mg iron, 1 mg vitamin B12 daily and 500 mg calcium,

800 U-combinations of vitamin D, multivitamin, and mineral preparations (1.4 mg thiamine, 400 µg folate, and 14 mg zinc) twice daily. All patients were also prescribed proton pump inhibitors during the first two months postoperatively.

The medical intervention started with a very low energy diet (VLED) period for twelve, sixteen or twenty weeks depending on the starting weight (BMI 35−39.9, 40−49.9 or ≥50 km/m², respectively) during which the patients were recommended to consume 450−800 kcal and 1.5−2 l of fluids daily (146). At baseline, two, five, eight, and twelve weeks, patients had check-in visits with a nurse. After the VLED, patients underwent a supervised 12-week reintroduction period. During this period, a very-low energy meal was replaced monthly with a new alternative, ranging from 300 to 475 kcal, for breakfast, lunch, and dinner. Subsequently, patients continued with a personalized energy-restricted diet based on the Nordic Nutrition Recommendations, with a daily intake of 1400−1600 kcal (15−20% energy from protein, 30% energy from fat, and 50−55% energy from carbohydrates). Additionally, after 6 and 12 months, patients were eligible to receive additional treatments such as glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, orlistat, or a combination of bupropion and naltrexone if deemed suitable.

At baseline and two-year follow-up, demographic data, previous blood work results from electronic medical records, study-specific blood samples, and validated questionnaire data were collected. The assessments were also carried out at the five-year follow-up visit and will be performed at the ten-year time point as well.

3.1.4. Study IV

Study IV comprised data of four IBS studies (n=646, Rome III and IV) and one population-based study. The patients were recruited at the Gastroenterology Outpatient Clinic in Gothenburg and Stockholm. The patient data was derived from two observational cohort studies (NCT01252550) (147, 148) and two randomized controlled trials (NCT02107625 and NCT02970591) (129, 149). Patients included before and after 2016 were diagnosed with IBS according to the Rome III and Rome IV criteria, respectively. In the four patient studies, the following in- and exclusion criteria overlapped. Patients who had major psychiatric, liver, neurological, or cardiac diseases, as well as coeliac disease, inflammatory bowel disease, known food allergies, or other severe GI conditions that could account for GI symptoms, were deemed ineligible for the study. Instructions were provided to patients to either discontinue the use of any IBS medications or continue their usage if they had been on a stable dosage for at least one month prior to inclusion. Exclusion criteria also stated that patients following a restrictive diet (e.g., vegan, gluten-free, low FODMAP diet), being pregnant or lactating, and having a BMI<18 kg/m^2 or >35 kg/m^2 were ineligible.

The sex- and age-matched (±3 years) control data (n=646) used in this study was obtained from a population-based study conducted by Statistics Sweden (SCB) (150). The study investigated the national

dietary intake of 1,797 Swedish individuals (representative of the Swedish population) and took place between 2010 and 2011. Initially, participants were sent invitations through postal mail, and subsequently, an interviewer from SCB contacted them to provide further details about the study. Those who expressed their consent were then provided with additional information both through mail and during subsequent phone conversations. Participants reported everything they ate and drank during four consecutive days in a web-based food diary and completed a questionnaire with about 50 questions (which was not utilized in study IV).

3.1.5. Study V

Finally, study V included consecutive patients with a DGBI (n=927, physician diagnosed) recruited at ten different secondary and tertiary care neurogastroenterology facilities in Eastern and Western DGBI research centers across the globe (**Figure 9**). Complete data collection took place during this PhD project. Five centers were situated in the Eastern region (China, Singapore, Japan, Malaysia, and Australia) and another five in the Western region (Belgium, Bulgaria, Italy, France, and Slovakia). At each center, a maximum of 250 participants were allowed to be enrolled and participating centers were encouraged to include the complete range of DGBI types. Patients were ineligible for the study if they had a diagnosed organic GI condition or another significant organic disease (e.g., diabetes, inflammatory bowel disease, or active malignancy) that could account for their GI symptoms. Additionally, individuals with a history of relevant GI surgery, major confounding conditions (such as psychiatric disorders or substance abuse), pregnant or lactating females, and those who had used opioids within one month prior to the study were also excluded.

Patients were requested to fill out a comprehensive survey once, which aimed to evaluate Rome IV DGBI diagnoses and the occurrence of GI symptom patterns. The survey was created by building upon the original Rome IV questionnaire, incorporating supplementary standardized questions specifically addressing the relationship between GI symptoms and meals, bowel movements or passing flatus.

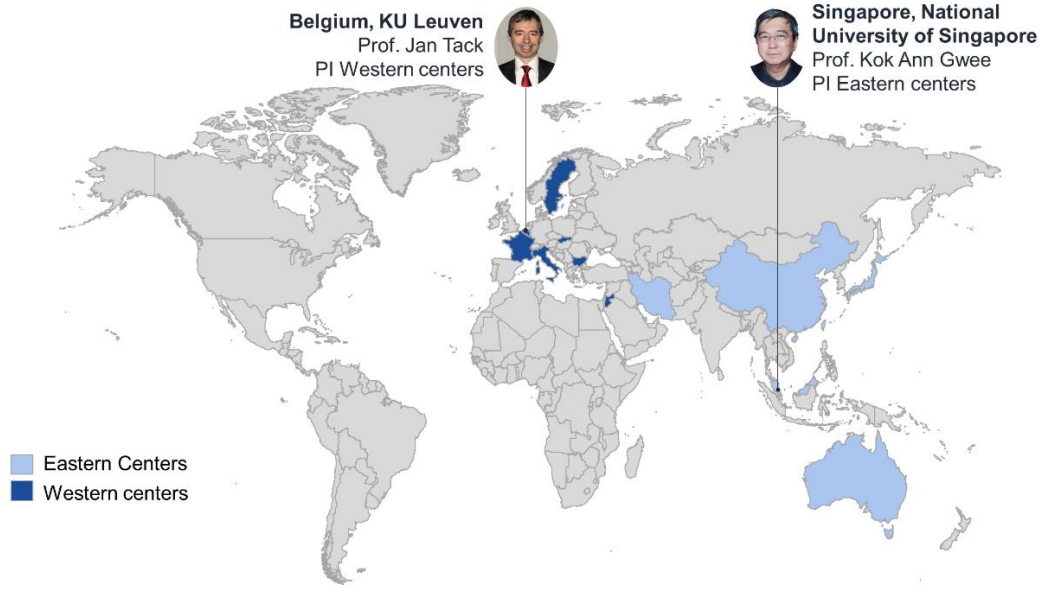

Figure 9. *Participating centers of the AEGIS study. (While all participating centers were included, not all of their data was utilized in study V due to practical limitations regarding data sharing.)*

3.2. Questionnaires

3.2.1. DGBI diagnoses and GI symptom frequency

Patients included in studies before 2016 were diagnosed with a DGBI according to the Rome III criteria and after 2016 the Rome IV criteria were used (1, 151). The Rome diagnostic criteria are assessed with the diagnostic Rome questionnaire and can assess the presence of over thirty disorders. In studies I, III, and V, nearly all parts of the questionnaire were evaluated, except for the gallbladder subset. In studies II and IV only the IBS criteria were used. The Rome III and Rome IV criteria for IBS are displayed in **Table 2** (4).

Table 2. *The Rome III and Rome IV diagnostic criteria for IBS.*

Rome III	Rome IV
Recurrent abdominal pain or discomfort at least three days/month in the last three months associated with two or more of the following criteria:	Recurrent abdominal pain on average at least one day/week in the last three months, associated with two or more of the following criteria:
1. Improvement with defecation	1. Related to defecation
2. Onset associated with a change in frequency of stool	2. Associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool	3. Associated with a change in form (appearance) of stool
Note: Symptom onset at least 6 months prior to diagnosis	

According to Rome Foundation recommendations, patients reporting celiac disease, GI cancer, or inflammatory bowel disease or patients with a self-reported history that could represent organic or structural reasons for their symptoms should be excluded from all DGBI diagnoses. Hence, in the included studies, patients were either asked to report the presence of any comorbidities at baseline or medical records were consulted.

The Rome diagnostic questionnaire also assesses the frequency of various GI symptoms. These symptoms were; sensations such as a lump in the throat, chest pain behind the breastbone, heartburn, difficulty swallowing, feeling full after meals, early satiety, pain and burning in the upper abdomen, nausea, vomiting, regurgitation, excessive belching, bloating or abdominal distention, biliary pain, unintentional stool leakage, discomfort, pain or pressure in the rectum unrelated to bowel movements, hard or lumpy stool, having less than three bowel movements/week (without the use of laxatives or enemas), straining during bowel movements, and a sense of incomplete bowel emptying. To assess these symptoms, the questionnaire included single-item questions structured as follows: "How often did you experience a specific symptom in the last 3 months?" The responses were recorded on either a 9-point Likert scale ranging from zero “never” to eight “multiple times per day or all the time”, or an 11-point Likert scale representing the percentage of times or instances, with 0% and 100% as the extreme points, in increments of 10%.

3.2.2. Enhanced Asian Rome IV Questionnaire

The Enhanced Asian Rome IV Questionnaire (EAR4Q) is an updated and expanded version of the EAR3Q, which was developed through a consensus process involving Asian experts in DGBI familiar with the Rome criteria (152). For study V, the EAR4Q was developed using a similar consensus process, but with the inclusion of both Asian and Western DGBI researchers.

In the initial phase of EAR4Q development, the wording of the EAR3Q items was modified to align with the Rome IV criteria while still considering the appropriateness of the questions in describing symptom patterns among Asian patients. Subsequently, a thorough review of the Rome IV was conducted, addressing each question individually. New questions were created for symptoms where the existing questions were deemed insufficient in capturing patients' and physicians' current clinical encounters. Additionally, systematic questions were added to assess the relationship (worsening or improvement) between each symptom and factors such as meal intake, bowel movement, and passing of flatus focusing on the use neutral terms to describe patients' symptom experiences.

All original Rome IV questions were retained, and new questions were positioned directly after each corresponding original Rome IV question to ensure compatibility and facilitate comparison with previous studies. The merged version of Rome IV questions with Asian-adapted questions and newly developed items was referred to as the EAR4Q. In the final phase, the EAR4Q was translated into new languages following the guidelines provided by the Rome Foundation (153).

3.2.3. GI symptom severity

In projects that included IBS patients, we used the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) and/or the Gastrointestinal Symptoms Rating Scale for IBS (GSRS-IBS) to assess IBS symptom severity. The IBS-SSS measures the frequency and severity of abdominal pain, the severity of bloating, bowel habit dissatisfaction, and daily life interference of IBS symptoms using a visual analogue

scale with a 10-day recall period (154). A sum score with a range from 0 to 500 is used to classify IBS symptom severity: <75 points “no symptoms”, 75–174 points “mild”, 175–299 points “moderate” and ≥300 points “severe”. The GSRS-IBS questionnaire contains thirteen items about the past week that are rated on 7-point Likert scale where one means “no symptoms” and seven “severe symptoms” (155). There are five GSRS-IBS subscales with their respective sum score ranges: pain (2–14), bloating (3–21), constipation (2–14), diarrhea (4–28), and satiety (2–14).

3.2.4. Stool frequency and consistency

In projects that contained only IBS patients, the patients’ bowel habits were recorded in a 10-day or 14-day stool diary based on the BSF scale (156). Patients reported the frequency and scored the consistency of their bowel movements during ten or fourteen consecutive days. Scoring the consistency was based on the BSF scale. The outcomes of the diary determined whether patients were categorized into IBS-C, IBS-D, IBS-M, or IBS-U. The last two groups could be combined into one group; IBS-nonCnonD.

3.2.5. Non-GI symptom severity

3.2.5.1. Non-GI somatic symptoms: PHQ−12

The measurement of non-GI somatic symptoms was conducted using the Patient Health Questionnaire (PHQ)−12, a modified version of the PHQ−15 excluding three questions related to GI symptoms (157, 158). Participants rated their symptoms on a scale ranging from zero, indicating "not bothered at all", to two, indicating "bothered a lot", with a recall period of two weeks. The total PHQ−12 score, ranges from 0 to 24, and is derived by summing the individual symptom scores, where higher scores indicate a greater burden of non-GI somatic symptoms. One specific item assesses menstrual cramps or other period-related issues, which means that women could potentially have higher PHQ−12 sum scores overall.

3.2.5.2. Psychological distress: PHQ−4, PHQ−9, Hospital Anxiety and Depression Scale, The Beck Anxiety Inventory

The PHQ−4 questionnaire consists of four items designed to measure the presence of anxiety and depression symptoms experienced within the past two weeks (159). The responses to each item are scored on a scale ranging from zero, indicating "not at all," to three, indicating "nearly every day." By summing up the scores, one can calculate separate scores for anxiety, depression, and overall psychological distress. Higher cumulative scores indicate a greater severity of psychological distress.

The PHQ−9 was employed to measure the levels of depression (160). This questionnaire consists of items asking respondents about their experiences over the past two weeks, including their level of interest in activities, difficulties with sleeping, and presence of suicidal thoughts. Each item is scored on a scale of zero, representing “no presence of the symptom” to five, representing “the symptom occurring nearly every day”. The total scores are used to categorize depression levels as follows: none or minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27).

Another questionnaire assessing both anxiety and depression, was the Hospital Anxiety and Depression Scale (HADS) with a separate anxiety (HADS−A) and depression (HADS−D) subset (161). The HADS is a self-report screening scale consisting of fourteen items. Each of the two 7-item scales has a score range from zero to twenty-one, where higher scores indicate greater severity. A score of eleven is commonly regarded as the threshold for identifying clinically significant anxiety or depression.

Lastly, the Beck Anxiety Inventory (BAI) questionnaire was used to assess how often and how severe common anxiety symptoms occurred within a 7-day period (162). Examples of these symptoms include trembling hands and the inability to relax. Each item in the questionnaire is given a score ranging from zero, indicating “no presence of the symptom” to three, indicating “severe presence of the symptom”. Based on the total scores obtained, anxiety levels are categorized as follows: minimal (0–7), mild (8–15), moderate (16–25), and severe anxiety (26–63).

3.2.5.3. GI-specific anxiety

The Visceral Sensitivity Index (VSI), consisting of 15 items, was utilized to measure anxiety specifically related to GI symptoms (163). Each item in the questionnaire is rated on a 6-point Likert scale, with low scores indicating a strong agreement with the statements and high scores indicating a strong disagreement. A higher total score (ranging from 0 to 75) on the VSI suggests a more severe level of GI-specific anxiety.

3.2.6. Quality of life

3.2.6.1. PROMIS Global-10

To evaluate the overall QoL among the participants, the PROMIS Global-10 questionnaire was employed (164). This questionnaire consists of nine statements related to subjective QoL, social interactions, physical functioning, mental well-being, and fatigue. Participants rate these statements on 5-point Likert scales. Additionally, the tenth question assesses overall pain and was rated on an 11-point Likert scale. From the responses, two total scores were calculated: one for physical QoL and another for mental QoL. Higher scores on these scales indicate a better QoL.

3.2.6.2. The EuroQol five-dimensional questionnaire

Another assessment of current health-related QoL was conducted using the EuroQol five-Dimensional questionnaire (EQ-5D) (165). The EQ-5D consists of five dimensions: mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression. Each dimension presents a set of statements, and respondents are required to choose the statement that best describes their situation. The scores for each dimension are then transformed into an index score that ranges from zero (representing a state as severe as being dead) to one (representing full health). This index score provides a summary of the respondent's overall health-related QoL.

3.3. Dietary intake assessment (study II and IV)

3.3.1. 4-day food diaries

Patients diagnosed with IBS maintained a record of their dietary intake using paper-based 4-day food diaries. They documented their food consumption from Wednesday to Saturday or for an unspecified four-day period (the last four days of the study screening period). A dietician provided instructions to the patients, advising them to follow their regular eating habits and carefully record all food items along with their precise quantities, using grams or household measures.

In study IV, the control group had two options for documenting their 4-day food intake. They could either utilize a web-based platform connected to an extensive food item database or participate in a retrospective phone interview using a 48-hour recall method. The control group received instructions similar to those given to the patients. The starting day of the food diary was randomized, encompassing Tuesday, Wednesday, Saturday, or Sunday, ensuring an equitable distribution of weekdays and weekend days. In cases where controls consumed a food item that was not listed in the database, they were requested to select the closest related item available.

The food diaries of the control group were directly entered into a software known as the Riksmaten method (version 04.1), which is connected to a Swedish food composition database provided by the Swedish Food Agency (166). This software facilitated automated estimations of nutrients and energy content. Dieticians manually entered data from the paper-based food diaries of the IBS patients into an extended version of the Dietist XP 3.1 software, linked to the same Swedish food composition database but with an additional FODMAP database add-on (167). This enabled the calculation of the average daily FODMAP intake, covering excess fructose, galacto-oligosaccharides, fructans, polyols, and lactose. The average daily excess fructose intake was determined by subtracting the average daily fructose intake from the glucose intake. When patients recorded composite foods, the dieticians separated the items into their individual ingredients before entering the information into the software.

3.3.2. Diet quality

To evaluate adherence to healthy eating patterns, an index known as the Diet Quality Index for Swedish Nutrition Recommendations (DQI-SNR) was used, which was developed and validated by Drake et al. (168). This index assesses adherence to the Swedish national dietary guidelines, which are based on the Nordic nutrition recommendations.

The DQI-SNR considers various components, including the intake of saturated and polyunsaturated fatty acids, fish, fiber, fruit and vegetables, and sucrose. For each component, adherence or nonadherence to the dietary recommendations is scored as one or zero, respectively (**Table 3**). These scores are then summed up to obtain a total score ranging from zero to six, with a score of six indicating excellent adherence and good diet quality.

Table 3. *DQI-SNR components with cut-offs*

Index component	Cut-off
SFA (E%)	≤14
PUFA (E%)	5−10
Fish and shellfish (g/week)	≥300
Dietary fiber (g/MJ)	≥2.4
Fruit and vegetables (g/d)	≥400
Sucrose (E%)	≤10
Note: SFA; saturated fatty acids, E%: energy percentage, PUFA: polyunsaturated fatty acids, adherence adds one point to the total score, non-adherence zero points.	

Since only a few individuals reported consuming less than the recommended 10% of energy from saturated fatty acids, the cut-off limit for saturated fatty acids was adjusted by adding one standard deviation (SD) and set to 14%. This adjustment was in line with the index developers' recommendations. Additionally, for dietary fiber intake, only the lower intake limit was considered, instead of the originally proposed range, and the cut-off limit was set to ≥2.4 g/MJ.

To facilitate a more understandable interpretation of the DQI-SNR, the participants were categorized into groups based on their diet quality. These groups included good diet quality (DQI-SNR: 4−6), moderate diet quality (DQI-SNR: 2−3), and poor diet quality (DQI-SNR: 0−1).

3.3.3. Diet diversity

To assess diet diversity, the intake of twenty-seven food groups was analyzed. These food groups were created by categorizing all consumed food items into specific groups using the classification system provided by the Swedish Food Agency (169, 170). The food groups included alcohol, bread, butter, cereal, coffee, condiments/spices/pickles, dairy, drinks, eggs, fast food, fish, fruit, juice, lactose-free dairy, legumes, margarine, meat, mixed dishes, nutritional supplements, nuts and seeds, oil, potatoes, salty snacks, sweet dishes and desserts, tea, vegetarian dishes, and vegetables. If the average intake of a particular food group over a period of four days was greater than zero, individuals received a score of one. A total score was then calculated by considering all twenty-seven food groups, resulting in a score ranging from zero to twenty-seven. Higher scores indicated greater diet diversity, reflecting a wide range of food choices, while lower scores suggested a more monotonous diet with limited variety.

3.4. Data analyses

3.4.1. Comparisons

3.4.1.1. 95% Confidence Intervals

To compare proportions in big data studies I and III, 95% confidence intervals (CI) were used instead of the traditional p-value approach. This decision was deliberate, as the large sample sizes would likely result in many statistically significant p-values, even for small differences. To illustrate this, let's consider an example from study I: 57.2% (56.2, 58.2) of individuals with no meal-related abdominal pain, 54.6% (53.7, 55.5) of those with occasional pain, and 58.8% (57.6, 60.1) of those with frequent pain were female. The p-value for the difference between these proportions was less than 0.05, indicating a significant difference among the three groups. However, focusing solely on the p-value does not provide a clear understanding of the magnitude or practical significance of the difference. It simply confirms our expectation that individuals with frequent GI symptoms are more likely to be female, as we know that the prevalence ratio of DGBI in females vs males is 2:1. In this example, the practical significance of the differences in the proportion of females among our three meal-related pain groups may be limited. Although the proportions differ, the observed differences are very small, particularly between the group with no meal-related abdominal pain and the group with frequent pain.

It may be tempting to interpret the 95% CI as a 95% chance that the true proportion lies within that range. However, the correct interpretation is as follows: if we were to repeat the survey 100 times, we would expect 95 of those instances to yield confidence intervals that contain the true population-level proportion. In reality, we only have one sample, and we can be 95% confident that the interval contains the true population-level of e.g. the proportion of females in the group with frequent meal-related abdominal pain.

Reporting statistical findings using the p-value approach informs readers about whether an estimate is zero or not. However, knowing that an estimate is non-zero may not have practical significance in many contexts. Additionally, a statistically significant finding may not be practically meaningful, despite readers perceiving it as such. In addition, reporting statistical findings using the 95% CI approach provides insight into the range of possible estimates and the practical significance of the findings. However, despite best efforts, readers may still misinterpret the 95% CI from a technical standpoint. Misinterpretation is likely in both cases, but the misinterpretation associated with the confidence interval approach is relatively harmless, whereas misinterpretation of the p-value approach can be more substantial.

3.4.1.2. Standardized mean differences

Another less classical approach used in this thesis to compare differences was the standardized mean differences method calculated with Cohen’s d formula in study IV to compare the food intake of patients with IBS vs. controls (171). Similarly to using the CI as described above, the standardized mean

differences approach allows you to draw conclusions not only about “non-zero differences”, but also provide some information about effect sizes. The effect sizes in study IV were interpreted using Cohen's guidelines, where a small effect size is d=0.2−0.4, a medium effect size is d=0.5−0.7, and a large effect size is d≥0.8.

3.4.2. Analysis of variance with linear contrast analysis

Another noteworthy data analysis approach is the analysis of variance with linear contrast analysis used in study III to examine the potential association between experiencing symptoms of DGBI across multiple GI regions and its impact on health outcomes (171). This approach allowed us to explore a linear trend and determine the effect size, which was quantified using partial eta squared (η^2). Effect sizes can range from small to medium (η^2=0.047–0.11) or be classified as large (η^2>0.11).

3.4.3. Regression analyses

This thesis utilized both ordinal and linear regression models to examine various research questions. These regression models are powerful statistical tools that enable us to explore relationships, make predictions, and understand the factors influencing the outcomes of interest.

Ordinal regression is a statistical method employed to examine and model the association between an ordinal dependent variable and one or more independent variables. It proves particularly useful when analyzing ordered categorical outcomes with three or more categories, such as Likert scales. An example in this thesis is the DQI-SNR, scored from zero to six, used as outcome, and IBS patient characteristics included as independent factors in order to assess which IBS characteristics can be associated with good and poor diet quality patterns. Ordinal regression aims to estimate the odds of an outcome belonging to each category based on the values of the independent variables. It enables the analysis of both the direction and strength of the relationships between the independent variables or predictors and the ordinal outcome. By estimating the coefficients, ordinal regression provides valuable information about the influence of the independent variables on the likelihood of the dependent variable falling into a higher or lower category.

Linear regression assumes a linear relationship between the predictors and the outcome variable. The goal of linear regression is to estimate the coefficients (slope and intercept) that best fit the data and can be used to predict the values of the dependent variable based on the values of the independent variables. To calculate the coefficients, the method of least squares is used, which minimizes the sum of squared differences between the observed and predicted values. An example of this thesis includes the association between the intake of different food groups (independent variables) and the IBS symptom severity (linear) as outcome.

In study I and II, mixed ordinal and linear regression were used. Mixed ordinal and linear regression differs from normal regression by incorporating random effects in the model. This allows for the

consideration of both fixed effects, which capture the relationships between predictors and the outcome, and random effects, which account for the variability between different groups or subjects. By incorporating random effects, mixed regression provides a more flexible and comprehensive approach for analyzing ordinal and linear outcomes in the presence of clustered or nested data structures. In study I and II the random effects of the variable 'country' and 'time' were considered, respectively.

3.4.4. Factor analysis

In study V, DGBI symptom patterns were investigated using factor analysis, a statistical approach that groups variables with strong correlations. The factor analysis consist of an initial exploratory factor analysis (EFA) and a confirmatory factor analysis (CFA). The estimation of latent factors, which represent groupings of symptoms, was approached using an EFA model. Maximum likelihood estimation with robust standard errors was employed, allowing for the inclusion of cases with missing values on symptom items. To ensure independence of the resulting factor scores, factor loadings were reported with rotation using the Varimax method. The determination of the initial number of factors was carried out through parallel analysis. This involved comparing the observed eigenvalues, which indicate the amount of explained variance, with the average eigenvalues obtained from randomly simulated data. The largest factor solution was selected based on the last factor whose observed eigenvalue exceeded that of the simulated data.

Model fit, a measure of how well the empirically derived symptom groupings represent the observed pattern of correlations between symptoms, was evaluated using a measurement model, specifically a CFA model. The root mean square error of approximation (RMSEA) and Chi-Square fit test (compared to the saturated model) were reported as indicators of model fit. Optimal values for RMSEA are <0.05, while $p>0.05$ and a ratio of Chi-Square statistic to degrees-of-freedom <5 are desirable. Configural invariance was used to assess the equality of model parameters between Eastern and Western samples (172). Factors were labeled based on the variance explained, such as factor 1 (F1) accounting for more variation in symptoms between individuals than factor 2 (F2).

3.4.5. Software and statistical help

The analyses were performed using various types of software including IBM SPSS Statistics (version 26 and 29 SPSS, Chicago, IL, 187 USA), R (version 4.1.1 and 4.2.2) and R Studio (version 1.3.1093 and 2023.03.0), and SAS 9.4 (SAS Institute, Cary, NC). Due to the extensive size of the dataset in study I, it was essential to have a trained statistician approved by the Rome Foundation who conducted all the analyses. The complexity and magnitude of the data made it unsuitable for an untrained individual to work with, emphasizing the need for expertise in handling and analyzing such a large dataset. After internally discussing the research questions, general approach, and hypotheses, J.P.H. was the approved statistician who performed the analyses. Together, we interpreted the initial findings. The analyses in study II was performed with the help of L.V.O., the statistician who taught me how to use and write

SAS scripts and interpret finding of mixed linear regression models. Study III and IV contained analyses completely performed by me, with advise from J.P.H. in study IV. M.J. performed the advanced statistical analysis included in study V, the factor analysis. Together, we interpreted the findings.

While I required assistance with many of the analyses incorporated in this thesis, it is of great significance to acknowledge and express gratitude to the senior statisticians who dedicated their time to explaining the statistical methodologies and teaching me how to independently apply them. Their guidance and expertise have contributed significantly to my knowledge and understanding in this field, and I am truly grateful for their support.

4. RESULTS AND DISCUSSION

4.1. Study I

4.1.1. What is the global prevalence of meal-related abdominal pain?

In total, 52% of the global population reported to experience abdominal pain in the last three months. In 18% and 23% of the cases this abdominal pain was never and occasionally meal-related, respectively, with occasionally being defined as 10−40% of the time with abdominal pain. In the global population, approximately 11% of individuals frequently experienced meal-related abdominal pain (defined as ≥50% of the time with abdominal pain). We chose these particular frequency cutoffs to enhance the understandability of the variable of interest. **Figure 10** illustrates the varying occurrence of frequent abdominal pain related to meals among the countries involved, highlighting noticeable disparities.

Figure 10. *Global prevalence of frequent meal-related abdominal pain.*

These findings indicate that a substantial proportion of the global population associates abdominal pain with meal intake. Not all these individuals will experience abdominal pain to the extent that they will consult medical care for it, but suggestively, a subgroup of these individuals might be in need of medical support. Frequent meal-related abdominal pain was found to vary in prevalence, ranging from 5% in Italy to 18% in Turkey. Earlier studies have demonstrated significant variation in the prevalence of DGBI across different countries (2, 173-175). The differences in prevalence across countries might originate from sociocultural factors (176-179), including national differences in healthcare services (180) and patients' perception of the sensation of (abdominal) pain. In turn, these could also influence symptom reporting (181, 182). Secondly, the differences in the formulation or wording of both "meal-related" and "abdominal pain" can yield discrepancies in interpretation (183). Lastly, international differences of dietary habits and beliefs are relevant when interpreting these differences across countries (184, 185).

4.1.2. Which individuals in the general population frequently experience abdominal pain related to meals?

Thirteen percent of the female global population reported frequent meal-related abdominal pain compared to 9% of the male population. The prevalence was 15% in the age group of 18−29-year-olds compared to 10% in the 45−59-year-olds. Individuals experiencing frequent meal-related abdominal pain were more likely to meet the diagnostic criteria for DGBI in all anatomical regions of the GI tract compared to subjects with no or occasional meal-related abdominal pain. The proportion of patients with frequent meal-related abdominal pain was highest in the esophageal DGBI, functional dysphagia (14%), gastroduodenal DGBI, functional dyspepsia (29%), and bowel DGBI, IBS (25%). In addition, there was a notable correlation between the growing number of DGBI diagnoses across different anatomical GI regions and an accompanying upward trend in the proportion of individuals with frequent meal-related abdominal pain. The subgroup with frequent meal-related abdominal pain was also more likely to experience other GI symptoms, primarily other food-related symptoms, such as postprandial fullness (OR = 2.27), and early satiety (OR = 2.04), and other aspects of pain, such as general abdominal (OR = 3.77), and biliary pain (OR = 2.37). The individuals with frequent meal-related abdominal pain exhibited a greater burden of psychological distress (β = 0.24), non-GI somatic symptoms (β = 0.35) as well as a poorer physical (β = -0.22) and mental QoL (β = -0.17). Moreover, a higher proportion of individuals with frequent meal-related abdominal had used healthcare service for bowel problems before. Hence, the individuals who reported frequent meal-related abdominal pain were more often females, younger, were more likely to fulfill diagnostic DGBI criteria across all GI regions, use healthcare services for their GI symptoms, and had a higher burden of other GI and non-GI symptoms.

Multiple characteristics of this subgroup were unsurprising. We hypothesized that the subgroup with frequent meal-related abdominal pain would exhibit the characteristics typically observed in patients with a DGBI. The majority of DGBI exhibit a higher prevalence in females compared to males, with a female-to-male ratio of approximately 2:1 and decrease with age (186, 187). This discrepancy can be attributed to various factors including psychological (188, 189), social (190, 191), dietary habits (192, 193), and biological differences (194-199) between sexes and age groups. The individuals experiencing frequent abdominal pain related to meals exhibited a higher likelihood of meeting diagnostic criteria for DGBI. Moreover, this subgroup was more prone to experiencing additional GI symptoms, along with a notable psychological burden, diminished QoL, and increased healthcare utilization. These findings might suggest that this particular subgroup represents a distinct patient group characterized by a more severe and diverse symptom pattern, ultimately leading to overall worse health outcomes (200, 201).

Patients reporting meal-related symptoms may find significant benefits from a comprehensive care approach that includes dietary and lifestyle guidance, alongside pharmacological and psychological interventions (202). This comprehensive approach has the potential to optimize treatment efficiency and

enhance overall outcomes by addressing the diverse needs of patients in a unified manner. **Table 4** summarizes the strengths and limitations of study I.

Table 4 . *Strengths and limitations of study I.*

Strengths	Limitations
The study population was highly representative of the global population and uniformly collected across the high number of participating centers.	The cross-sectional nature of the data did not allow us to study potential fluctuations of the symptom patterns over time.
The study survey was designed by a team of international DGBI experts with cultural adaptations and linguistic validations.	The anonymized data collection prevented us from accurately identifying and confirming clinical histories or conducting medical tests to exclude alternative diagnoses that could account for the observed symptom patterns.
The survey included quality checks to identify and exclude inconsistent and inattentive responders from the analyses, resulting in the acquisition of high-quality data.	The analysis of meal-related abdominal pain in the study focused solely on its frequency, using a single item from the survey. However, it would have been valuable to also evaluate the severity and overall impact of this symptom, as well as other meal-related symptoms.

4.2. Study II

4.2.1. Can psychological, nutritional, or microbial factors predict how IBS patients respond to the NICE and/or low FODMAP diet?

Study II identified several psychological, nutritional and microbial factors that could predict symptom-specific response to the traditional NICE guidelines and/or the low FODMAP diet. Symptom-specific response was investigated by examining the abdominal pain, constipation, diarrhea, and bloating responses over time during the 4-week interventions. A lower dysbiosis index ($p = 0.05$), an indicator of less severe dysbiosis, and higher total energy intake ($p = 0.03$) at baseline predicted a better abdominal pain response to both diets **(Figure 11)**. In the NICE diet treatment arm, higher baseline intake of oligosaccharides (i.e., galacto-oligosaccharides and fructan) emerged as a distinct predictor for better pain improvement ($p = 0.02$). However, this correlation could not be observed in the low FODMAP treatment arm ($p = 0.49$). A lower initial dysbiosis index also predicted better constipation improvement during both diets when focusing on the improvement of constipation ($p = 0.01$). Higher baseline disaccharide (i.e., lactose) intake could predict a better constipation improvement to NICE diet ($p = 0.01$), which was absent in the low FODMAP diet ($p = 0.46$). For the improvement of diarrhea, no predictors were identified. Worse bloating improvement in both diets could be predicted by more severe baseline psychological distress ($p = 0.03$). Higher baseline oligosaccharide intake was associated with worse bloating improvement during the low FODMAP intervention, which was not observed during the NICE diet.

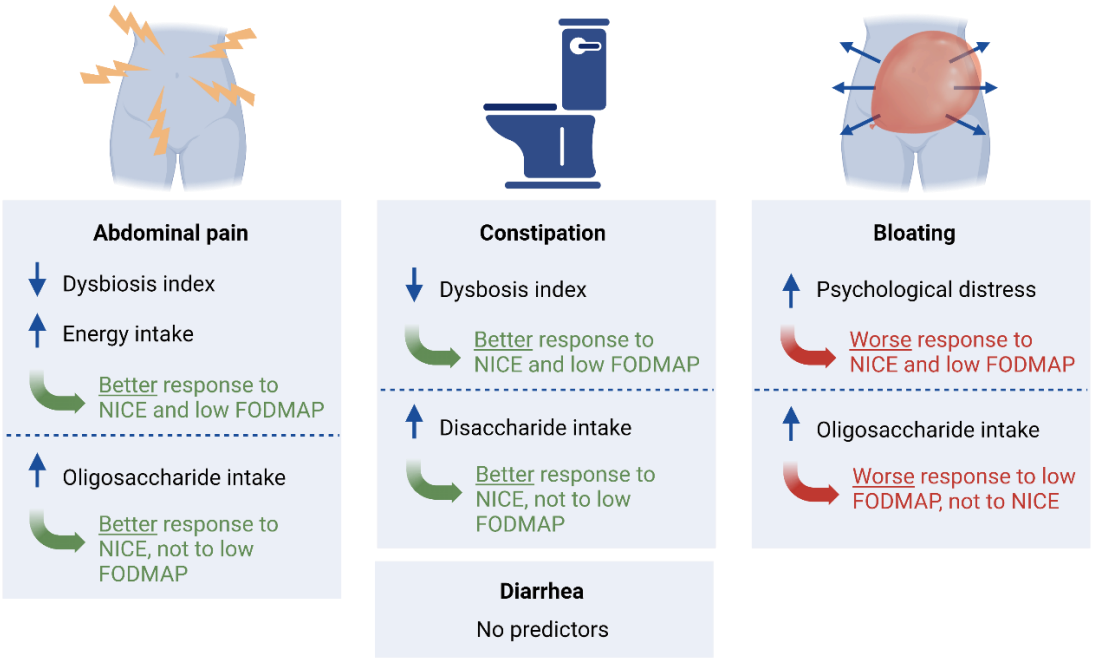

Figure 11. *Overview of the symptom-specific predictors of response to the NICE and/or the low FODMAP diet.*

Overall, our results indicate that patients with milder clinical characteristics exhibited a more favorable response to the dietary interventions. These less severe clinical features included higher energy intake and markers suggesting a potentially healthier microbial composition. Prior research has indicated that lower energy intake may serve as a potential indicator of severe food avoidance and restriction (134). Additionally, altered microbiota have the potential to trigger mucosal innate immune responses, resulting in increased epithelial permeability, activation of nociceptive sensory pathways, and dysregulation of the enteric nervous system (203). Consequently, both of these factors have been linked to more severe symptoms in IBS. Interestingly, the limited previous studies investigating predictors of dietary treatment response have shown the opposite when it comes to the baseline IBS symptom severity. Patients with more severe baseline IBS symptoms and microbiota profiles resembling a more pathogenic phenotype have been identified as having a higher likelihood of responding positively to the low FODMAP diet (89, 91). It is unclear where these discrepancies between finding come from, but they might be attributed to methodological differences, including differences in study populations, primary outcome, and the assessment of microbial factors.

The presence of significant psychological distress has also been associated with more severe IBS symptoms (204) and might serve as a negative indicator for implementing the NICE or low FODMAP diet. It could be suggested that patients with greater psychological distress, potentially related to their relationship with food, may exhibit hypersensitivity towards dietary modifications and could be at a higher risk of developing eating disorders (135, 136).

Lastly, our study showed that patients with a higher baseline intake of specific FODMAP groups may experience better outcomes when following the NICE diet, whereas following a low FODMAP diet may not lead to the same results. Our findings suggest that adhering to the originally proposed treatment algorithm, i.e. recommending the traditional IBS diet first and only transitioning to the more restrictive low FODMAP diet when symptoms are not adequately relieved, may be most appropriate (61). Patients who have not identified FODMAPs as triggers and do not actively avoid or restrict them in their habitual diet may not derive significant benefits from the highly restrictive low FODMAP diet. Instead, these patients may benefit more from alternatives such as following the traditional IBS guidelines or adopting a "gentle" low FODMAP diet that focuses on reducing the intake of the most prominent trigger food groups rather than complete elimination (137, 138). These patients could potentially also benefit from behavioral or psychological therapies, such as gut-directed hypnotherapy (205). Overall, these finding again underline the importance on being mindful when choosing management strategies for this heterogeneous patient population. **Table 5** provides an overview of the study's strengths and limitations.

Table 5. *Strengths and limitations of study II.*

Strengths	Limitations
The outcome, i.e. response to dietary intervention, was not dichotomized into "responders" vs. "non-responders". Instead, the study considered the improvement of various IBS-specific symptoms to be able to contribute to more individualized treatment algorithms.	We used a convenience sample for these analyses. The design of the study did not consider sample size calculation for these analyses.
We preselected potential predictors from three different domains that are highly important in the pathophysiology of IBS, i.e., psychological, microbial, and nutritional factors.	

4.3. Study III

4.3.1. What is the prevalence of DGBI symptoms among individuals with obesity?

Symptoms compatible with a DGBI could be identified in 61% of our study cohort with obesity. When focusing on disorders categorized by anatomical GI region, we found that bowel disorders (38%) were the most prevalent, followed by gastroduodenal (27%), esophageal (23%), and anorectal disorders (9%). Among the specific disorders, IBS (21%) emerged as the most frequently occurring, followed by nausea and vomiting disorders (17%), and functional heartburn (14%). In study III, Rome III criteria were used to diagnose DGBI symptom profiles, which was the most recent version during the data collection. The findings from study III revealed a significantly high DGBI prevalence among individuals with obesity given that the estimated global prevalence of DGBI, stands at around 40% (2). To our knowledge, study III is the first study to evaluate the prevalence of the complete range of DGBI symptoms profiles in obesity. However, previous studies have investigated the link between IBS and obesity, but have yielded inconsistent results. Current associations observed in the literature are either positive, positive in a certain subgroup, insignificant (after adjustments), or negative. Study III indicated that the prevalence

of IBS is higher among individuals with obesity compared to the general population, which is estimated to be around 10% or 4%, either using the Rome III or Rome IV criteria, respectively (2). Notably, nausea and vomiting symptoms have been consistently positively associated with obesity (111), with a primary focus on vomiting (109, 206, 207). Multiple studies have also demonstrated that obesity or a higher BMI is a risk factor for the development of GERD or GERD-related symptoms, as observed in functional heartburn (109, 207-214). Hence, according to study III, DGBI symptom profiles across all anatomical GI regions seem to be apparent in obesity.

4.3.2. Which individuals with obesity encounter symptoms of DGBI and what is the effect of having multiple GI regions affected by a DGBI?

Individuals with obesity were more likely to have comorbid DGBI symptom profiles when they were female, had more severe anxiety and depression, and a poorer QoL (all $p < 0.001$). BMI or the degree of obesity was slightly lower ($p = 0.03$), and the LDL cholesterol, and HDL cholesterol levels (both $p = 0.04$) slightly higher in individuals with comorbid DGBI symptoms compared to without, but these differences were judged clinically irrelevant.

Within the subgroup of individuals with obesity and comorbid symptoms compatible with a DGBI, 57% had one, 30% two, and 14% three or four GI regions affected by DGBI symptoms. **Figure 12** shows the proportion of patients with and without overlapping conditions. In total, 44% exhibited overlapping DGBI symptom profiles, with the most prevalent combination involving symptoms in both the gastroduodenal and bowel regions (8%). This was followed by overlapping symptoms in the esophageal and bowel regions (7%), and the esophageal and gastroduodenal regions (7%).

With increasing number of affected GI regions, there was a significant linear trend associated with worse health outcomes, including more severe psychological distress, and poorer QoL (**Figure 13**). No trend was observed for degree of obesity or BMI.

Thus, in our study, comorbid DGBI symptoms in obesity were linked to poorer health outcomes, which is not surprising as there exists a general inverse association between multimorbidity or comorbidity and QoL (215). Similar findings have been documented in the DGBI literature, where the presence of DGBI affecting multiple anatomical regions of GI tract is associated with increased severity of GI and non-GI symptoms (200). Furthermore, the absence of a clinically relevant relationship between degree of obesity and comorbid DGBI symptom profiles has also been observed in patients with obesity who have comorbid GERD symptoms (210). As a result, healthcare providers should be mindful of the potential coexistence of DGBI in obesity, as considering this aspect when evaluating treatment options may lead to improved health outcomes.

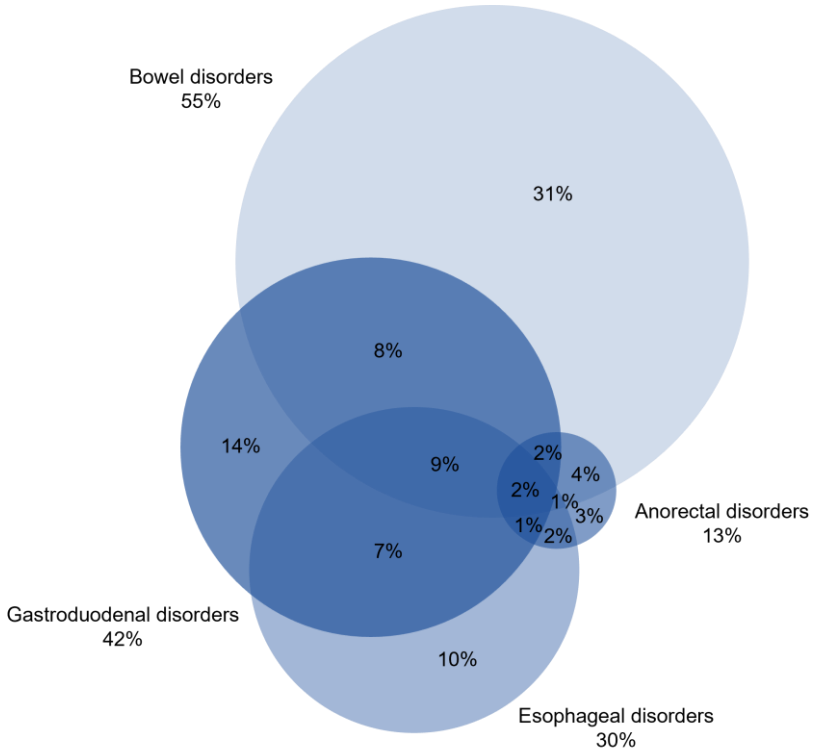

Figure 12. *Venn diagram showing overlap of DGBI regions within patients with obesity and comorbid DGBI. Not shown in the figure: overlap between esophageal and bowel disorder (7%), and gastroduodenal and anorectal disorders (2%). The areas within the diagram are not entirely proportional to the numbers.*

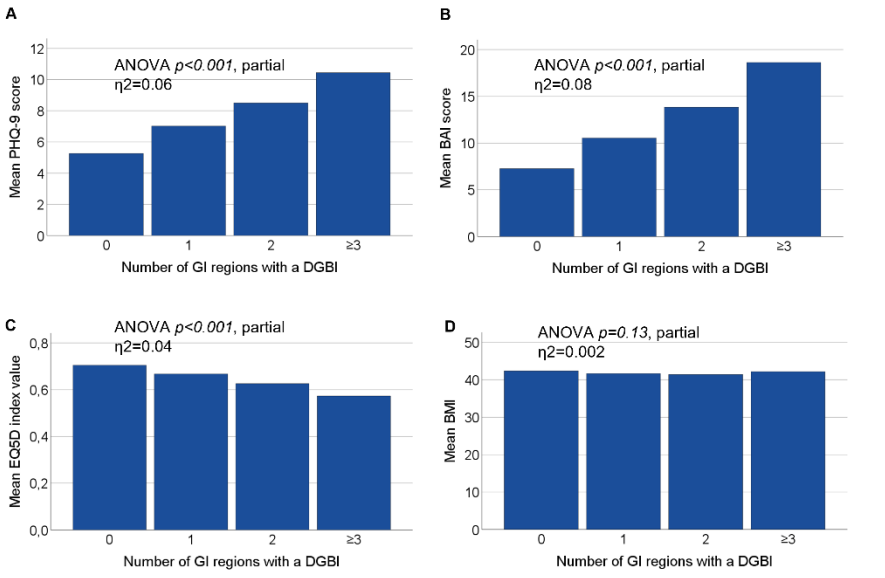

Figure 13. *Association between the number of GI regions affected with a DGBI and health outcomes.*

4.3.4. What is the impact of obesity treatment on DGBI symptoms?

Two years after obesity treatment, the proportion of patients with symptoms compatible with a DGBI decreased from 61% to 53%, including individuals who had a DGBI diagnosis at baseline, but also patients with a new DGBI diagnosis. Among the patients who initially presented with a DGBI symptom profile, 38% no longer exhibited those symptoms after obesity treatment. Conversely, among the patients who did not have a DGBI symptom profile at baseline, 40% developed a new DGBI symptom profile at the follow-up assessment. In general, there was a substantial decrease in the proportion of patients with esophageal disorders (from 24% to 15%) following obesity treatment. We observed a slight decrease in the prevalence of gastroduodenal disorders (from 27% to 25%) and bowel disorders (from 38% to 34%). The proportion of patients with anorectal disorders remained consistent at 8% after obesity treatment. Similar findings were observed following both medical treatment and RYGB. However, a different pattern emerged after SG treatment. Specifically, the prevalence of esophageal, bowel, and anorectal disorders remained stable after obesity treatment, while there was a significant increase in the prevalence of gastroduodenal disorders.

The differences observed in the SG treatment arm, including the significant increase in gastroduodenal and some esophageal disorders, such as functional heartburn, have been described in previous research indicating that acid-reducing medication use, heartburn, and regurgitation are increased after SG (114). This is in line with the SG clinical guidelines describing GERD as a contraindication and the need for acid-reducing medication after SG. After undergoing RYGB, functional dysphagia was the only esophageal disorder that exhibited an increase in prevalence. This finding aligns with a previous study that demonstrated a significant increase in dysphagia in obese individuals after RYGB surgery (216). In general, bowel disorders showed a slight decrease in our patient cohort. This could be attributed to dietary changes, which occurred not only in the medical treatment group but also in patients who underwent surgery. It is likely that patients shifted from a high-fat to a low-fat diet, as a high-fat diet stimulates the release of bile acids acting as a natural laxative. Therefore, the observed decrease in diarrhea was expected. However, constipation symptom patterns appeared to increase across all treatment arms, with the most pronounced increase observed after SG. This increase in constipation prevalence in obesity may be partially explained by polypharmacy (217). However, further research is needed to determine whether these surgical techniques alone or the weight loss resulting from the surgery are the main factors driving the improvement and worsening in DGBI symptoms. **Table 6** lists the strengths and limitations of study III.

Table 6. *Strengths and limitations of study III.*

Strengths	Limitations
Study III had a large sample size providing greater statistical power and an increase in generalizability of the findings.	Our strength in using the Rome III questionnaire is also a limitation, since we were not able to use the more recent Rome IV criteria.
Instead of concentrating on individual DGBIs or specific GI symptoms, we established DGBI symptom profiles across the entire GI tract.	DGBI symptom profiles were not confirmed by a physician.
Due to the longitudinal design of the BASUN study, we were able to examine DGBI symptom profiles both before and after three different types of obesity treatment.	The treatment options were not randomized across individuals
We used the validated Rome III questionnaire to identify symptoms compatible with a DGBI.	

4.4. Study IV

4.4.1. Do patients with IBS have different dietary habits compared to individuals in the general population?

When comparing dietary habits of patients with IBS and sex- and age-matched controls from the general population, several differences could be observed. In both groups, the intake of macronutrients adhered to the national nutrition recommendations apart from the patients eating less energy from carbohydrates than recommended (**Figure 14**). Compared to the control group, patients showed a lower consumption of carbohydrates, particularly mono- and disaccharides such as sucrose, as well as dairy products, mixed dishes (e.g., lasagna, pasta salads), coffee, potatoes, vegetarian dishes, sweet dishes and desserts, and bread (effect sizes d = 0.2−0.7). Conversely, patients had higher intakes of fat, saturated and mono-unsaturated fatty acids, lactose-free dairy, oil, salty snacks, nuts and seeds, butter, juice, and exhibited higher total energy intakes and diet diversity scores (effect sizes d = 0.2−0.7).

Previous studies, in line with our results showed that patients consumed less carbohydrates than controls, which they potentially compensated by increasing their fat intake (218, 219). Surprisingly, patients with IBS had a higher total energy intake compared to controls, contradicting previous findings (218-220). However, methodological differences in data collection, including the inclusion of more weekend day records in the patient data, and variations in under-reporting between the control sample and patients' food diaries entered by trained dietitians, may explain this discrepancy. Additionally, the large sample size may have led to statistically significant but clinically insignificant differences. Patients with IBS demonstrated dietary patterns consistent with their recognition of common triggers for IBS. They consumed lower amounts of dairy, sweet dishes and desserts (particularly lactose-containing ones), and caffeinated coffee compared to controls. Patients also had a lower intake of bread, potentially high in fructans or gluten, aligning with previous findings on gluten consumption in more severe IBS cases (221). They successfully substituted dairy with lactose-free alternatives, leading to higher diet diversity scores.

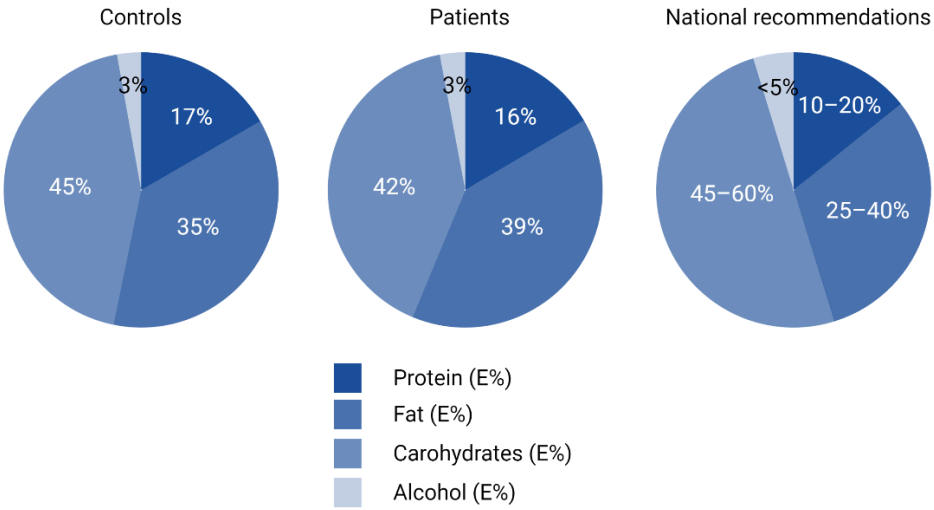

Figure 14. *Energy percentage of macronutrient intake in controls vs. patients with IBS vs. the recommendations.*

Among the patients, 19% were categorized as having poor diet quality, 52% as moderate, and 29% as good, while among the controls, the corresponding percentages were 18% for poor, 47% for moderate, and 35% for good diet quality. The comparison showed a trend towards statistical significance (p=0.06). Further analysis revealed that the proportion of controls in the good diet quality category was significantly higher than the proportion of patients in the poor and moderate quality categories (p<0.05). When looking into the different components of the diet quality index (DQI-SNR), less patients with IBS adhered to the recommended intake of saturated fatty acids and more patients followed the intake recommendation of sucrose (**Table 7**). Significant differences in adherence to saturated fatty acids were found between patients and controls in both males and females. Female patients showed higher adherence to sucrose compared to female controls. More females adhered to the recommendations bout fiber intake and the adherence was higher in the female control group compared to the female patient group.

Similar findings have been reported in previous studies (219), including a study linking poor diet quality to increased gas-related symptoms and decreased quality of life (222). Although the differences in diet quality between patients and controls were small in our study, it suggests that better diet quality may be relevant to manage IBS symptoms.

Table 7. *Differences in adherence to the DQI-SNR components in patients with IBS vs. controls (both n = 646)*

Index component	Adherence		p-value
	IBS	Controls	
SFA (E%)	41.8% (38.0, 45.7)	58.8% (54.0, 62.6)	**<0.001**
PUFA (E%)	61.1% (57.3, 64.9)	59.1% (55.2, 63.0)	0.46
Fish (g/week)	35.8% (32.1, 39.6)	38.7% (34.9, 42.6)	0.27
Dietary fiber (g/MJ)	38.1% (34.3, 42.0)	43.3% (39.5, 47.3)	0.05
Fruit and vegetables (g/d)	13.8% (11.2, 16.7)	16.3% (13.5, 19.3)	0.21
Sucrose (E%)	82.5% (79.4, 85.4)	70.7% (67.1, 74.2)	**<0.001**

4.4.2. Are there specific patterns between dietary habits and symptoms in patients with IBS?

Having more severe IBS symptoms were associated with higher intakes of protein, dairy, and vegetables. Additionally, less diverse dietary patterns, lower total energy intake, lower intakes of carbohydrates, sweet dishes and desserts were also linked to having more severe IBS symptoms. Lower diet diversity score, total energy intake, alcohol intake, fish intake, sweet dishes, and desserts were predictors of more severe GI-specific anxiety, while higher intakes of protein, drinks, meat, and excess fructose were also associated with greater anxiety (**Figure 15**). Finally, we examined the relationship between IBS characteristics and diet diversity, which may indicate food avoidance and restriction. In the multivariable regression model, female sex, more severe IBS symptoms, and non-GI somatic symptoms were significantly associated with lower diet diversity scores. However, when investigating diet quality as an outcome, no significant predictors of patient's diet quality were found in the multivariable model.

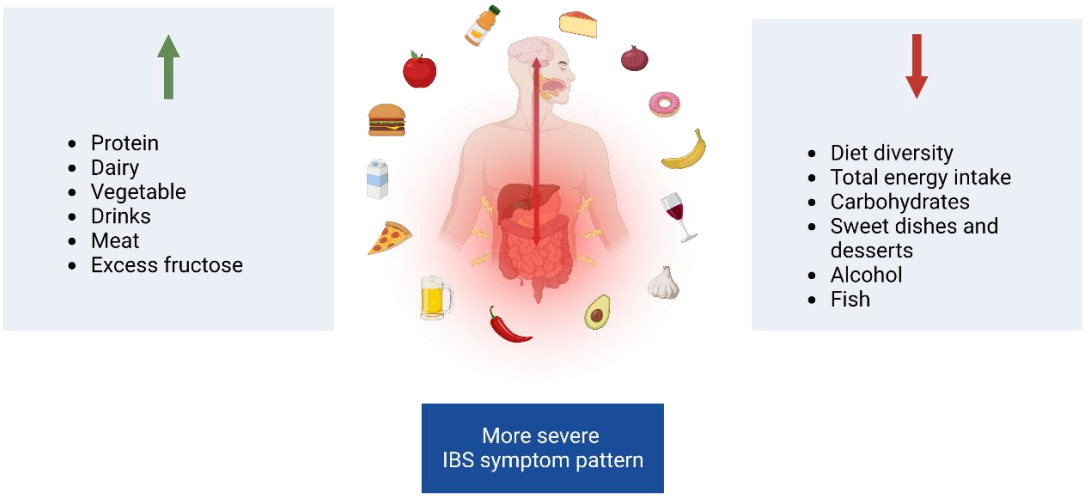

Figure 15. *Dietary factors associated with a more severe IBS symptom pattern.*

The association between lower energy intake and lower diet diversity, as an indicator of potential food avoidance and restriction, and more severe IBS symptoms has been observed before by Melchior et al (134). Further investigation is needed to explore potential predictors of diet quality, as the existing literature is limited and inconsistent (219, 222), and our analysis did not provide sufficient information in this regard. Patients with more severe symptoms exhibited poorer diet quality and diversity. Similar findings exist in research on eating disorders, such as ARFID (134). The link between symptoms and food in IBS can lead to dysfunctional beliefs, including body dysmorphia from abdominal distention (223). Patients with a history of exclusion diets are more likely to have ARFID symptoms (224), and those with both IBS and eating disorders tend to exhibit a higher tendency to adhere rigorously to the low FODMAP diet (225). Further investigation is needed to understand the relationship between disordered eating and DGBI symptoms, as patients with DGBIs, particularly IBS, are clearly at risk for developing eating disorders (226). **Table 8** shows the key limitations and strengths of this study.

Table 8. *Strengths and limitations of study IV.*

Strengths	Limitations
This study had a large sample size, including a sex- and age-matched (±3 years) control group of which the data was partly collected at the same time in the same geographical region, i.e. Sweden.	The methodology of diet recording differed slightly between patients and controls.
We used a locally developed and validated measure of diet quality.	The two types of study participants might have had different incentives for study participation, potentially creating some bias in the results.
The 4-day dietary records captured both week- and weekend days leading to a correct representation of the habitual diet.	Our control sample did not include confirmed healthy controls, but individuals from the general population.

4.5. Study V

4.5.1. Do Eastern and Western patients with a DGBI experience symptom clusters involving multiple anatomical regions?

The EFA performed in study V revealed twelve distinct factors, or so called "symptom groupings". Together, these factors explained 50% of the response variance, with F1 (18%) explaining the most variance and F12 (1%) the least (**Figure 16**). F1, a globus factor, included all the original Rome IV globus items. F2 represented a symptom picture resembling IBS, with significant emphasis on bloating and flatulence triggered by meals and relieved by bowel movements or passing of flatus. It also included a minor association with meal-related abdominal pain. F3 encompassed various upper GI symptoms, predominantly regurgitation and vomiting. The fourth factor captured items from the original Rome IV subset of functional chest pain and heartburn. F5 connected upper (such as heartburn, postprandial fullness, nausea, regurgitation, and belching) and lower GI symptoms (including abdominal pain, constipation, diarrhea, and bloating) that were triggered by bowel movements or passing of flatus. F6 mainly revolved around meal-related diarrhea, which could be alleviated by bowel movements. The seventh factor exhibited significant associations with regurgitation, both relieved and triggered by bowel movements or passing of flatus. F8 shared a similar pattern to F5 but focused on the relief, rather than triggering, of upper (heartburn, postprandial fullness, epigastric pain/burning, nausea, and belching) and lower (abdominal pain and constipation) GI symptoms through passing of flatus. Bloating was the only symptom that found relief from bowel movements but not from passing of flatus. The ninth factor strongly correlated with all Rome IV constipation items, along with an additional item indicating constipation relieved by bowel movements. F10 corresponded to postprandial fullness relieved by bowel movements or passing of flatus. F11 represented IBS, characterized by abdominal pain relieved by bowel movements and associated with changes in stool consistency and frequency. Lastly, F12 displayed a distinct pattern of epigastric pain/burning, reflecting the Rome IV epigastric pain syndrome (EPS). However, in this EFA, unlike the Rome IV definition, EPS was also linked to altered bowel habits and triggered by meal intake.

Figure 16. *Twelve DGBI symptom groupings identified with factor analysis.*

The confirmatory model of the complete cohort matched well with the exploratory model for all twelve factors. Afterwards, we performed two separate CFAs on the Eastern and Western patient data to examine if all twelve symptom groupings are apparent in both Eastern and Western DGBI patients. These analyses showed that symptom groupings were consistent between regions, however the correlations between distinct symptom groupings were not.

The symptoms of F1, F6, F9, and F11 closely align with the Rome IV criteria for globus, functional diarrhea, functional constipation, and IBS, respectively. This finding, also identified in earlier factor analyses (227-231), further supports the individual classification of these specific disorders as within the Rome IV criteria. Factor 2, similar to factor 11, had limited correspondence with the Rome IV criteria. F2 emerged as a distinct factor resembling an IBS-like pattern characterized by meal-related bloating, flatulence, and abdominal pain. These symptoms could be alleviated by a bowel movement or passing of flatus. While previous reports have mentioned that some IBS patients experience worsening symptoms after meals (22, 232), our factor analysis distinguishes this pattern as a separate entity from IBS. In F2, the focus is on gas-related symptoms and meal-related abdominal pain, highlighting a specific physiological event, namely, meal intake. A similar meal-related bowel factor was observed in a study by Siah et al., which included Asian patients with a DGBI (233). This is a first indication that we observe symptom patterns transcending the classical Rome IV categorizations, i.e. disorders grouped according to distinct anatomical GI regions. F5, F7, F8, F10, and F12 combined upper GI symptoms together with lower GI symptom groupings or physiological events, contradicting previous findings that identified distinct upper and lower groupings (229). These symptoms were either triggered or worsened by bowel movements or passing of gas (F5), or they were relieved by them (F8). Accordingly, neural connections between distant regions of the GI tract, as well as broader responses to food intake and processing, appear to be factors that contribute to symptom triggering (23, 29, 234).

Lastly, F3 and F4 cover symptoms from various esophageal and gastroduodenal Rome IV diagnoses. Previous studies have already indicated overlap between gastric and esophageal motility as well as reflux events (235-238). It can be argued that some symptoms captured by these factors may be challenging for patients to distinguish. Additionally, regardless of the factor structure, there is a possibility of symptom overlap among different disorders due to shared underlying mechanisms. Research has demonstrated that overlapping disorders involving multiple GI regions are common and associated with increased health impairment (200, 201, 234, 239). These findings emphasize the importance of a comprehensive evaluation when managing patients with DGBI to identify all troublesome symptoms and administer appropriate therapy. However, current diagnostic and treatment guidelines provide limited guidance to clinicians dealing with patients with overlapping disorders. Considering the numerous symptom groupings observed in our study, extending beyond F3 and F4, which encompass GI symptoms across various anatomical locations, it is crucial for future research to delve deeper into this matter. **Table 9** displays study V's strengths and limitations.

Table 9. *Strengths and limitations of study V.*

Strengths	Limitations
Our factor analysis could contribute to the development of criteria beyond the Rome IV consensus. While our findings generally support the Rome IV criteria, they also offer valuable insights into specific areas that may benefit from further modifications.	The EAR4Q was not a validated questionnaire.
We included a large physician-diagnosed DGBI cohort with both patients from the Eastern region as well as the Western region. In addition, we developed the EAR4Q, a modified and extended version of the Rome IV that incorporates both Eastern and Western DGBI concepts applicable to this heterogeneous patient cohort.	Patients were recruited from specialist care settings, which may be associated with a more severe and more elaborate symptom burden.
We have collected data on various psychological parameters, QoL, GI symptom severity, medication use, previous investigations, and the presence of GI symptoms with explanatory pictograms. While discussing these data is beyond the scope of this paper, they present an opportunity for future analyses.	

5. CONCLUSIONS AND FUTURE PERSPECTIVES

DGBI are complex and multifactorial conditions that significantly affect patients' daily lives and society. During the last decade, research on DGBI has increasingly emphasized the role of gut luminal factors, particularly food, as potential contributors to the pathophysiology, as many DGBI patients report symptom associations with food intake. The studies included in this thesis investigate different aspects of food-related symptoms in DGBI patients, all aiming to enhance the overall understanding of the underlying mechanisms and improve the management of patients with a DGBI.

Study I contributed to the aim by investigating the global prevalence and burden of a common DGBI symptom, namely meal-related abdominal pain. In summary, the study highlighted a frequent meal-related abdominal pain prevalence of 11%, a significant portion of the global population. Identifying these individuals is crucial for assessing the scope of this issue, not only in the general population but also in clinical practice. By recognizing these patients, clinicians can develop management strategies that specifically address meal-related concerns, potentially involving the expertise of trained dieticians. To improve the management of this subgroup, further research focusing on meal-related GI symptoms beyond abdominal pain is necessary. Such studies will enable a comprehensive understanding of the complete symptom profile within this specific subgroup and enhance our knowledge of the underlying pathophysiological mechanisms.

Study II identified patterns of psychological, dietary, and microbial factors that could predict symptom-specific responses to two dietary interventions commonly prescribed to IBS patients; the traditional NICE diet and the low FODMAP diet. Our findings suggested that patients with a less severe clinical profile of IBS tend to exhibit a more favorable response to dietary interventions targeting specific symptoms. However, these findings need validation through larger prospective randomized controlled trials, preferably encompassing diverse treatment approaches that have demonstrated efficacy in IBS. Confirming these results could contribute to the development of personalized treatment algorithms for individuals with IBS.

In study III, we examined DGBI as a comorbidity to obesity. The study revealed that a significant number of individuals with obesity exhibit symptoms consistent with DGBI in various anatomical GI regions. The presence of comorbid DGBI symptoms in obesity is not correlated with the degree of obesity itself, but it is associated with lower QoL, increased psychological distress, and non-GI somatic symptoms. Obesity treatment is generally linked to a reduction in DGBI prevalence overall. However, the prevalence of certain specific DGBI symptom profiles may actually increase. Notably, the impact of obesity treatment on the prevalence rates were considerably different among the three obesity treatment options, medical treatment, RYGB, and SG. Future studies should concentrate on elucidating the underlying mechanisms by which GI symptoms arise and decrease following bariatric surgery.

The fourth study demonstrated notable distinctions in dietary patterns between patients with IBS and matched controls from the general population. More patients with IBS exhibited a poor diet quality compared to controls. Furthermore, within the patient group, it was observed that poorer dietary habits, such as reduced energy intake and lower diet diversity, were associated with more severe symptoms. These findings provide additional support for the multidisciplinary management of IBS patients, emphasizing the importance of addressing potential eating disorders and nutritional deficiencies. These findings once again emphasize the need for additional research on the connections between food and symptoms in IBS patients, as this could aid in the development of personalized management strategies.

Lastly, study V confirmed the presence of symptom groupings aligned with the Rome IV criteria, encompassing globus, functional diarrhea, functional constipation, and IBS. However, our analyses also identified symptom groupings that extend beyond the anatomical subdivisions outlined in Rome IV. Specifically, we observed an IBS-like factor characterized by meal-related bloating, flatulence, and abdominal pain. Additionally, we identified a factor encompassing both upper and lower GI symptoms associated with bowel movements and passing of flatus. We discovered a distinct grouping of upper GI symptoms linked to physiological events such as meal intake, defecation, and passing of flatus. These findings challenge the conventional symptom classifications of the Rome IV consensus and warrant further investigation. Future research should consider these results that challenge the anatomical-based groupings of the Rome IV classification scheme. These identified factors not only highlight the presence of overlapping conditions but also emphasize the need for in-depth exploration of the complete symptom profile this heterogeneous patient population experiences.

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CONTRIBUTIONS

Study I

E.C., C.M., J.A., J.P.H., S.S., H.T., and M.S. planned and initiated this particular analysis. E.C and J.P.H. conducted the analysis and interpreted the data before drafting the manuscript. L.V.O. provided advice on the analysis and interpretation of the data. E.C. drafted the manuscript. A.D.S., S.I.B., and O.S.P. designed and conducted the original epidemiology study and gathered the data. All authors critically revised the manuscript. H.T, J.T., and M.S. supervised the overall project. All authors read and approved the final manuscript.

Study II

Conceptualization, E.C., L.V.O. and M.S.; methodology, L.V.O. and E.C.; software, L.V.O.; validation, E.C., L.V.O., M.S. and S.N.; L.V.O. and E.C.; investigation, L.B., S.S. and S.B.; resources, M.S.; data curation, E.C. and S.N.; writing—original draft preparation, E.C.; writing—review and editing, all authors; visualization, E.C.; supervision, M.S., L.V.O., H.T., J.T., L.Ö.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

Study III

E.C., J.H., H.T., M.S. planned and initiated this particular analysis. E.C, J.H., M.B. conducted the analysis and interpreted the data before E.C. drafted the manuscript. G.H., K.M., M.E., B.E., L.F. designed and conducted the original BASUN study and collected the data. All authors critically revised the manuscript. J.T., H.T., M.S. supervised the overall project.

Study IV

E.C., S.N., S.S., H.T., M.S. planned and initiated this particular analysis. E.C and J.P.H. conducted the analysis and interpreted the data before drafting the manuscript. J.P.H. provided advise on the analysis and interpretation of the data. E.C. drafted the manuscript. All authors critically revised the manuscript. H.T, J.T., M.S. supervised the overall project.

Study V

E.C., F.C., J.T., K.A.G, K.T.H.S. planned and initiated this particular analysis. M.J. and E.C conducted the analysis and interpreted the data before drafting the manuscript. E.C. drafted the manuscript. L.H., T.B. J.L., C.M., G.G., K.H.C., K.X.H., S.M., K.T.H.S, P.L., P.B., G.H., N.K., M.C., B.A., H.S., M.S., T.U., P.H., H.S., P.A., M.S., M.J. collected the data. All authors critically revised the manuscript. J.T. supervised the overall project.

COI STATEMENT

Myself and the other co-authors involved in this PhD project declare no conflicts of interest. J.T. has given scientific advice to Adare, AlfaWassermann, Allergan, Arena, Bayer, Christian Hansen, Clasado, Danone, Devintec, Falk, Grünenthal, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Neurogastrx, Neutec, Novartis, Noventure, Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Truvion, Tsumura, Zealand, and Zeria Pharmaceutical; received research support from Shire, Sofar, and Tsumura; and served on the Speakers Bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda, Truvion, and Zeria Pharmaceutical. H.T. has received personal fees from Galapagos, Tillotts Pharma, Shire, Takeda, Cinclus Pharma, Dr Falk Pharma Gmbh, and Vipun Medical. M.S. has received grants and personal fees from Glycom and Danone Nutricia Research; personal fees from Ironwood, Biocodex, Adnovate, Arena, Tillotts, Kyowa Kirin, Takeda, , Abbvie, BioGaia, Cinclus Pharma, Pharmanovia, Sanofi, Janssen Immunology, Pfizer, Ferrer and the Falk Foundation; and grants from Genetic Analysis AS. G.H. reports personal fees from AstraZeneca and NovoNordisk. B.E. reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Mundipharma, NovoNordisk, RLS Global and Sanofi. C.M. has served as a consultant/advisory board member for Kyowa Kirin, Norgine, Biocodex, MayolySpindler, Tillots, and Ipsen. S.S. has served as an advisory board member for Takeda and speaker for Viatris. H.T. has served as an advisory board member/consultant for Almirall and Shire. L.V.O. is assistant research professor of the KU Leuven Special Research Fund (Bijzonder Onderzoeksfonds, BOF). A.D.S. has served as a consultant for Lapidot Israel and AbbVie-Israel. O.S.P. has received a research contract from the Rome Foundation during the conduct of the study and received a research contract from Glycom A/S and Royal DSM and personal fees from metaMe Health. S.S. has served as advisory board member for Takeda and speaker for Viatris. L.Ö. has received a financial support for research by Genetic Analysis AS, Biocodex, Danone Research and AstraZeneca and served as a consultant/advisory board member for Genetic Analysis AS, and as a speaker for Biocodex, Ferring Pharmaceuticals, Takeda, AbbVie, and Meda. All stated conflicts of interest are outside the submitted work.

COMPLETE LIST OF PUBLICATIONS

- Tack J, Schol J, Geeraerts A, Huang IH, Mori H, Scarpellini E, Sinonquel P, Carbone F, **Colomier E**, Geysen H, Jandee S, Moonen A, Pannemans J, Timmermans L, Van den Houte K, Verbeure W, Wauters L, Bisschops R, Hoffman I, Roelandt P, Rommel N, Simren M, Suzuki H, Tornblom H, Verbeke K, Vanuytsel T. A survey on the impact of the COVID-19 pandemic on motility and functional investigations in Europe and considerations for recommencing activities in the early recovery phase. Neurogastroenterol Motil. 2020 Jul;32(7):e13926.
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