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SYMPTOM PATTERNS IN IRRITABLE BOWEL SYNDROME

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

November 2019

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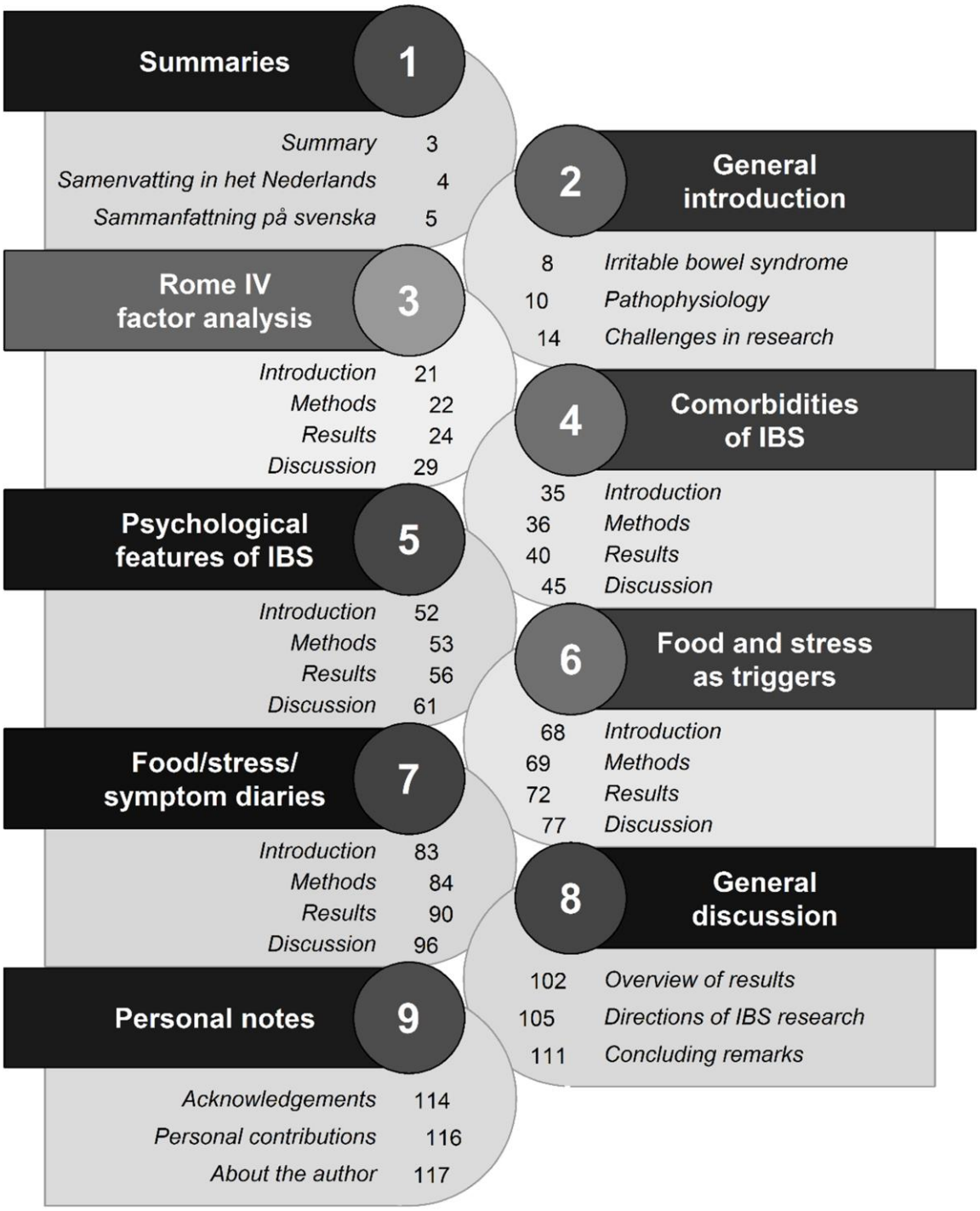
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Summary

Who has never had them: symptoms in the abdominal region, such as pain, bloating, constipation, and diarrhoea? These are common symptoms of irritable bowel syndrome (IBS). IBS affects 5-10% of the population, especially females between the age of 16 and 40.

The good news is that IBS is a benign disorder: IBS does not increase the risk of cancer, and symptoms are not progressive. The bad news is that impact on quality of life is high due to symptoms in the abdomen as well as elsewhere (e.g. joint pain) and psychological symptoms (e.g. anxiety) or even psychiatric disorders (e.g. anxiety disorders). Specifically, symptom-related anxiety is a predictor of more severe symptoms and worsening quality of life.

Why exactly do people have symptoms? In part, symptoms can be explained by lifestyle factors, mainly food and stress. Common food triggers have been described for diarrhoea (confectionery, coffee, spices), flatulence (onions, fruits, bread), bloating (late eating), and pain (late eating, rice, bread). Before we start dieting, however, two important remarks must be made:

- Intolerances to food and stress are very person-specific. Person-specific food-symptom and stress-symptom relations may be identified when a patient keeps a 3-week diary of food intake, stress, and symptoms. The computer analyses the diary for possible symptom triggers. Exclusion of personal triggers may lead to symptom improvement for a group of patients.
- There are many non-lifestyle factors that drive symptoms in IBS. These include the gut bacteria and immune system. Therefore, it is possible that a patient does not benefit from any dietary or psychological therapy.

This thesis leads to two research suggestions, both aiming for personalised management of IBS:

- Personal symptom triggers. Although we know that the food/symptom diary concept can generate personalised lifestyle advice, we still lack evidence that it actually improves symptoms. Patients who keep a diary and receive personalised lifestyle advice should be followed up to monitor symptom evolution. A great opportunity would be to combine it with smart devices that measure physiologic variables, as these may explain *how* a trigger leads to symptoms.
- Predictors of treatment response. For the patient, finding a treatment that works is currently a process of trial and error. There is a need for an evidence-based treatment algorithm, as this makes IBS management more efficient and teaches us about the underlying mechanisms.

Samenvatting in het Nederlands

Wie kent ze niet: maag-darmklachten zoals buikpijn, opgeblazen gevoel, obstipatie en diarree? Deze klachten (in afwezigheid van een duidelijke oorzaak) definiëren prikkelbare darm syndroom (PDS). Zo'n 5-10% van de bevolking heeft PDS, vooral vrouwen tussen de 16 en 40 jaar.

Het goede nieuws: PDS is goedaardig. Er is geen verhoogd risico op kanker en de klachten zijn niet progressief. Het slechte nieuws: PDS heeft een grote impact op het leven, niet alleen vanwege maag-darmklachten, maar ook door klachten elders (bv. gewrichtspijn) en psychologische klachten (bv. angst) tot zelfs psychiatrische aandoeningen (bv. angststoornissen). Specifiek is angst voor maag-darmklachten een voorspeller van ernstigere symptomen en verlaagde levenskwaliteit.

Waarom hebben mensen precies maag-darmklachten? Klachten worden deels verklaard door voeding en stress. Voedingstriggers zijn al veelvuldig beschreven voor diarree (snoepgoed, koffie, specerijen), winderigheid (uien, fruit, brood), opgeblazen gevoel (eten 's avonds laat) en buikpijn (eten 's avonds laat, rijst, brood). Maar eerst even twee belangrijke opmerkingen hierbij:

- Intoleranties voor voeding en stress zijn heel individueel. Persoonspecifieke triggers kunnen wellicht opgespoord worden middels een dagboek van voedingsinname, stress, en klachten (van ~3 weken). De computer analyseert het dagboek voor mogelijke triggers. Exclusie van die triggers zou dan kunnen leiden tot vermindering van klachten voor sommige patiënten.
- Er zijn ook veel niet-leefstijlfactoren van belang bij PDS. Dit zijn bijvoorbeeld de darmbacteriën en het immuunsysteem. Daardoor is het zeker mogelijk dat een patiënt niet reageert op welk dieet of psychotherapie dan ook.

Dit proefschrift leidt tot twee onderzoekssuggesties, beiden als opzet voor een individueel management van PDS:

- Individuele klachtentriggers. Hoewel het dagboek (voeding/klachten) kan leiden tot persoonlijk advies, missen we nog het bewijs dat het advies ook werkt. Graag zouden we het advies testen in patiënten die over tijd worden gevolgd. Idealiter combineren we dit met 'slimme meters', die allerlei fysiologische variabelen meten en zo kunnen verklaren *hoe* een trigger leidt tot klachten.
- Voorspellers van behandelingssucces. Voor de patiënt is het behandelingscircuit nog altijd een kwestie van uitproberen. Het wordt tijd voor een goed behandelingsalgoritme, omdat dit het management van PDS efficiënter maakt en het ons veel leert over hoe PDS werkt.

Sammanfattning på svenska

Alla känner till mag-tarmsymtom såsom ont i magen, uppblåsthet, förstoppning, och diarré. Dessa är vanliga symtom vid irritabel tarm (IBS). IBS påverkar 5-10% av befolkningen, framför allt kvinnor i åldern 16-40 år.

Den goda nyheten är att IBS är en godartad sjukdom: IBS ökar inte risken för cancer, och symtomen är inte progressiva. Den dåliga nyheten är att påverkan på livskvaliteten är stor, på grund av symtomen i magen och på andra ställen i kroppen (t.ex. ledvärk), samt psykologiska symtom (t.ex. ångest). Mer specifikt är symtomrelaterad ångest en prediktor för svårare symtom överlag och försämrad livskvalitet.

Varför har vi då mag-tarmsymtom? Delvis kan det förklaras av livsstilsfaktorer, främst mat och stress. Vanliga födoämnen som leder till symtom har beskrivits för diarré (sötsaker, kaffe, kryddor), gasbesvär (lök, frukt, bröd), uppblåsthet (äta sent på kvällen), och ont i magen (äta sent, ris, bröd), men innan man sätter igång och utesluter dessa produkter, måste två viktiga aspekter tas i beaktande:

- Intolerans mot mat och stress är mycket personspecifikt. Personspecifika relationer mellan mat, stress, och symtom kan möjligen identifieras med hjälp av en 3-veckors mat- stress- och symtomdagbok. Datorn analyserar dagboken avseende möjliga faktorer som utlöser symtom. Borttagande av dessa kan sedan potentiellt leda till symtomförbättring hos vissa patienter.
- Det finns även många icke-livsstilfaktorer som är relevanta vid IBS, såsom inkluderar tarmbakterier och immunsystemet. Därför är det möjligt att en patient inte drar nytta av dietjustering eller psykologisk terapi överhuvudtaget.

Denna avhandling leder fram till två forskningsuppslag, båda med relevans för individanpassad handläggning av IBS.

- Individuella faktorer som utlöser symtom. Även om 'mat- och symtomdagbokskonceptet' kan leda till individanpassade livsstilsråd, har vi ännu inga bevis för att det faktiskt förbättrar symtomen. Patient som för dagbok och får individanpassade livsstilsråd, bör följas upp för att utvärdera effekten av råden. En fantastisk möjlighet är att kombinera dagboken med 'smarta enheter' som samtidigt mäter och registrerar olika fysiologiska variabler, så att dessa kan förklara *hur* exv. mat eller stress utlöser symtom.

GENERAL INTRODUCTION

Prologue: a healthy dinner

"*But as for what I do and what I eat*", asked the engineer, "*why do they always tell us what to do?*" The health scientist nestled her spoon onto her quinoa-lentil salad: "*A healthy lifestyle reduces the risk for age-related diseases, you do know that, right?*" She reached for her handbag, which contained her brand new PhD thesis on nutrition and the metabolic syndrome. With it came a strip of pills, falling to the floor. Oh, horror. She grabbed it instantly, and, with a reddening face, stuck it in her pocket. When she returned from her next long bathroom break, the engineer, still enjoying the rich aftertaste of his *quattro formaggi*, asked: "*Are you alright? I was just a bit worried tonight about your… ehh… health.*"



Figure 1: Social occasions can be troublesome for people with gastrointestinal symptoms.

Health is not merely the absence of disease, but requires complete physical, mental, and social well-being[1]. The woman in the short story had gastrointestinal (GI) symptoms along with mental distress and social discomfort, and, with that, GI symptoms are a true health problem in every respect. The concept of a 'healthy lifestyle' was debated indirectly through the menu choices of the two. The scientist considered long-term health effects of the meal, whereas the engineer considered short-term health effects – besides mere preference. A paradoxical situation arises when foods typically promoted as healthful by scientists, dietitians, industry, and mass media (e.g. the quinoa-lentil salad in the short story) will trigger GI symptoms on the short term, and thus reduce one's physical, mental, and social health after all. In conclusion, the way in which we traditionally define a healthy lifestyle should arguably be reconsidered to cover the full definition of health, and to recognise GI symptoms as a major health problem affecting our lives today. With that in mind, this thesis discusses a disorder of GI symptoms: irritable bowel syndrome.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a disorder of abdominal pain and altered bowel habits. IBS is traditionally defined by the 'Rome criteria' (table 1).

Table 1: Definition and prevalence of IBS following the Rome II, III, and IV criteria.

Rome	Year	Symptom	Frequency	Associated with at least 2 of:	Prevalence
II[2]	1999	Abdominal pain or discomfort	≥ 12 weeks in past year	1. Relieved with defecation 2. Onset associated with a change in stool frequency 3. Onset associated with a change in stool form	9.4%[5]
III[3]	2006	Abdominal pain or discomfort	≥ 3 days per month	1. Improvement with defecation 2. Onset associated with a change in stool frequency 3. Onset associated with a change in stool form	11.3%[5]
IV[4]	2016	Abdominal pain	≥ 1 day per week	1. Related to defecation 2. Associated with a change in stool frequency 3. Associated with a change in stool form	5.7%[6]

Around 10% of the population has IBS[5-6]. However, IBS is more common in females than in males, and is typically diagnosed in females between 16 and 40 years of age (figure 2).

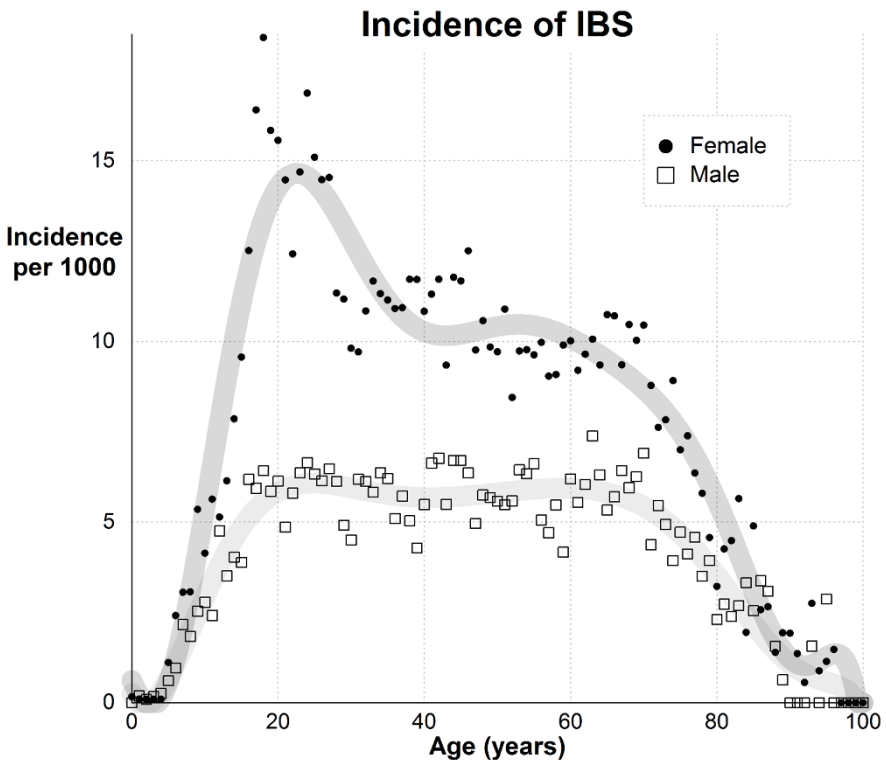

Figure 2: Incidence of irritable bowel syndrome (IBS) diagnoses in Flanders, Belgium. Data source: study 2.

Symptomatology and impact

IBS patients have abdominal pain and often diarrhoea, constipation, gas, and bloating, but usually other health problems as well (i.e. comorbidities). Comorbidities outside of the gastrointestinal (GI) tract include somatic symptoms (e.g. back pain) and psychosocial health problems (e.g. anxiety disorders). IBS is therefore more than a disorder of the GI tract alone. The total symptomatology of IBS has a strong impact on quality of life, both physically and mentally[7].

"My friends ask me to do things with them but 8 out of 10 times I turn them down because of symptoms I experience. I would love to go and have fun with them, but I feel as if my IBS is keeping me hostage!" [8]

"I was always used to doing so many different things. But now my body will tell me when I take on too much. I've got many limitations." [9]

IBS patients experience physical, mental, and social limitations, such as in social occasions[8] and everyday activities[9]. The diet is considered particularly important (figure 3), as most IBS patients feel unable to eat whatever and whenever they want. Finally, IBS also poses a burden to society through decreased work productivity (~40% loss in severe IBS)[10] and increased health care costs[11].

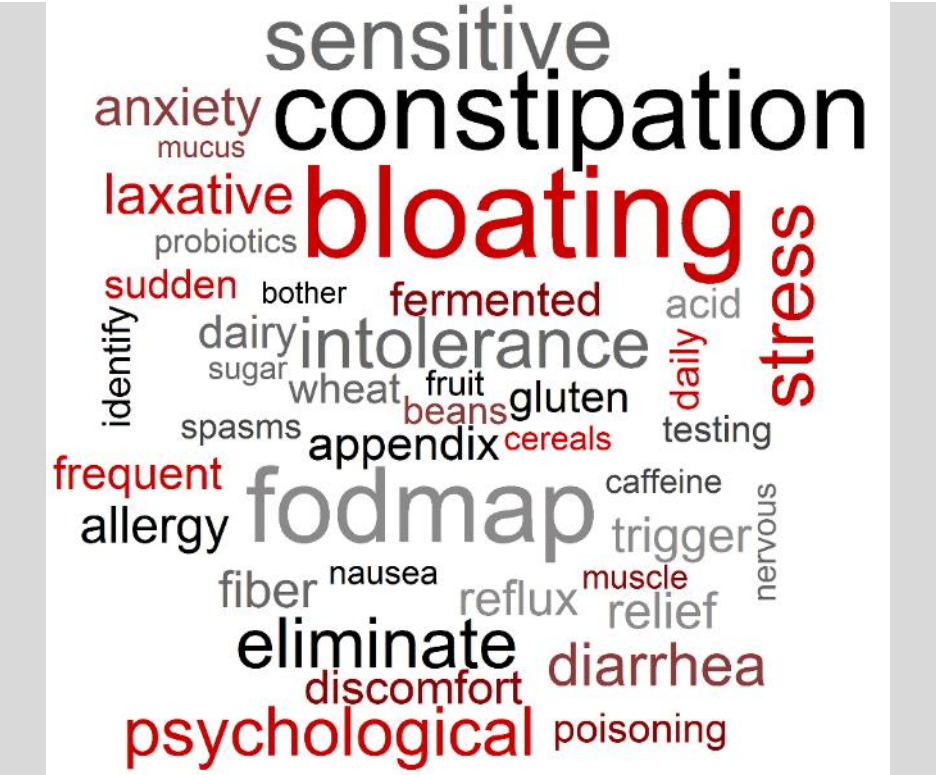

Figure 3: Word-cloud extracted from 91 IBS fora, adjusted for that of inflammatory bowel disease.

Pathophysiology

The 'why and how' of IBS can be seen as a puzzle of a million pieces. Figure 4 lays down some of the puzzle. From left to right, it covers predisposition and lifestyle factors (layer one), mechanisms (layer two), 'state changes' of the GI tract (layer three), and characteristic symptoms (layer four), leading to the clinical manifestation of IBS. It must be borne in mind, however, that IBS presents itself in a person-specific way, because not every piece is equally relevant for each IBS patient.

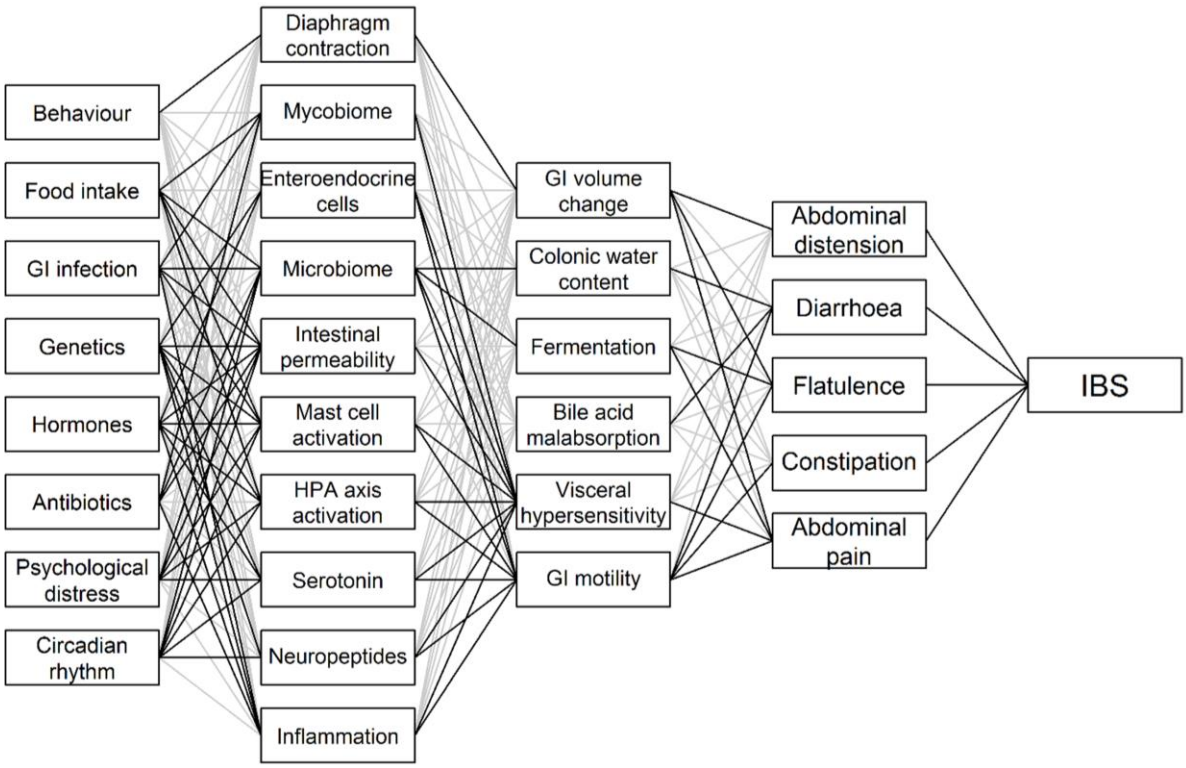

Figure 4: Pathophysiology of IBS, shown as a neural network. Darker lines represent some of the better characterised mechanisms.

IBS is a disorder of gut-brain interactions[4]. The gut signals to the brain about its current state, affecting hunger, satiety, but also mood[12]. The brain controls enzyme/mucus secretion and GI motility. GI motility is abnormal in many patients, leading to diarrhoea, constipation, and/or pain. It is controlled by various mechanisms (e.g. serotonin signalling, microbiota[13]), and also influenced by psychological distress[14], the diet, oestrogen[15] (explaining the sex difference, figure 2), the circadian clock[16], and genetics. Besides, most patients are hypersensitive to stimulation in the rectum[17] and colon[18] (i.e. visceral hypersensitivity), leading to pain. Why? Abdominal pain is sensed by receptors on nerve cells in the GI tract (e.g. transient receptor potential channels). In IBS, these pain-sensing receptors are larger in number, more sensitive, or more frequently stimulated, possibly by mast cells[19], which in turn can be activated by triggers such as psychological distress or food antigens[20].

The diet

The diet can trigger GI symptoms in many ways. First, through the *type* of consumed food. Caffeine, for example, is a stimulus that can accelerate GI motility[21]. Fatty foods are thought to increase visceral hypersensitivity on the short term[22], making one more susceptible to pain. Flatulence may be partially explained by so-called FODMAPs ('fermentable oligo-, di-, and monosaccharides and polyols': carbohydrates that are fermented into gas by the microbiota), while artificial sweeteners may draw water to the intestines and trigger symptoms in this way[23]. Food intolerance can also involve immune cells reacting to antigens from the diet[24]. Moreover, many plant-derived foods contain natural poisons potentially leading to GI symptoms (e.g. uncooked nightshades). Finally, the *style* of eating is a relevant factor, such as the eating environment and diet regularity (figure 5).

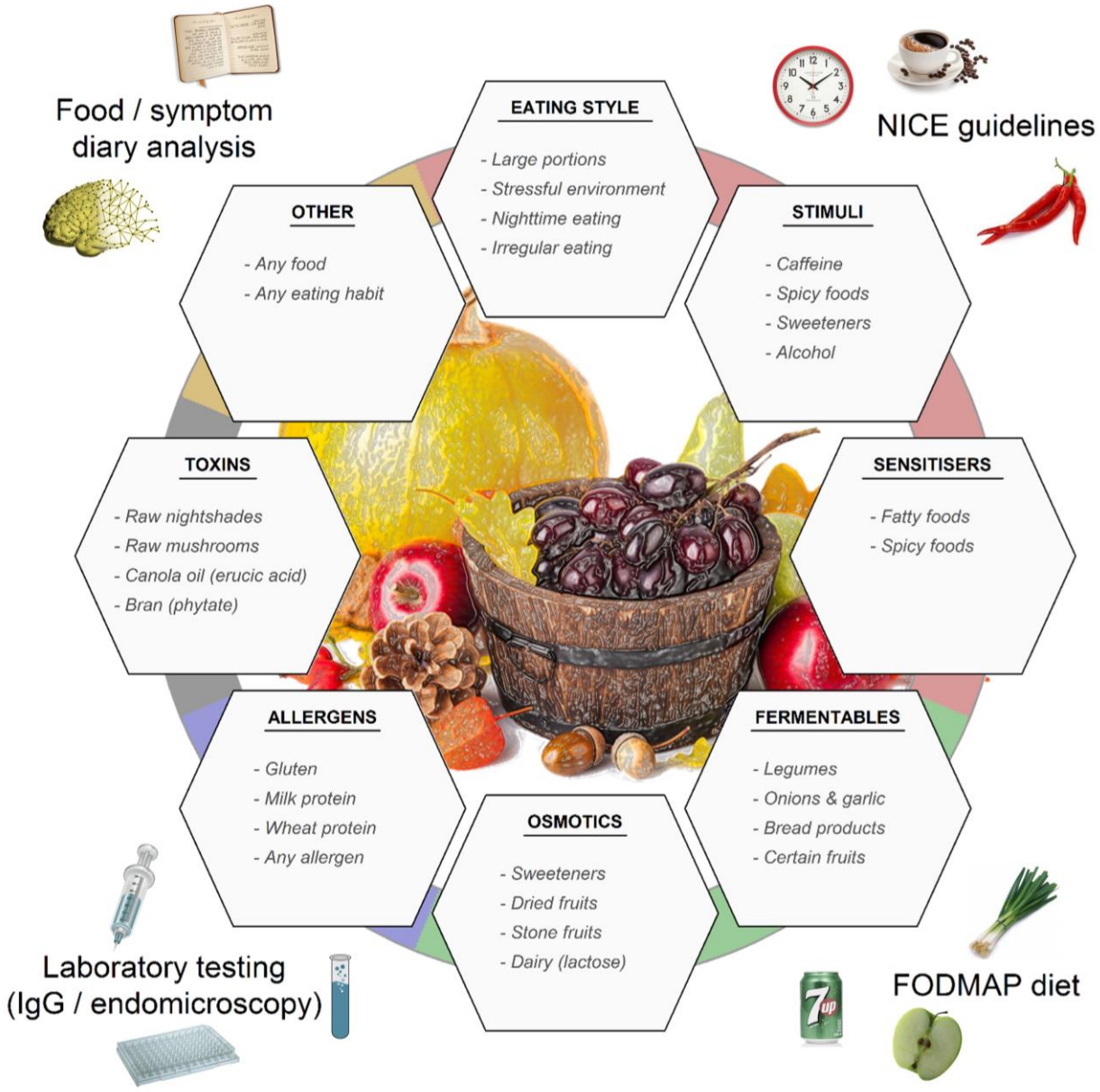

Figure 5: Mechanisms by which the diet can trigger GI symptoms, and some diet strategies that can be used to address these.

Psychological distress and disorders

Psychological distress can also trigger GI symptoms. On a stressful day, one has an increased chance of having GI symptoms[25]. GI symptoms can also lead to psychological distress. The association between psychology and GI symptoms can be explained by means of the so-termed 'gut-brain axis', illustrated in figure 6. However, the link between psychology and GI symptoms might also translate to alterations in the gut microbiota[26].

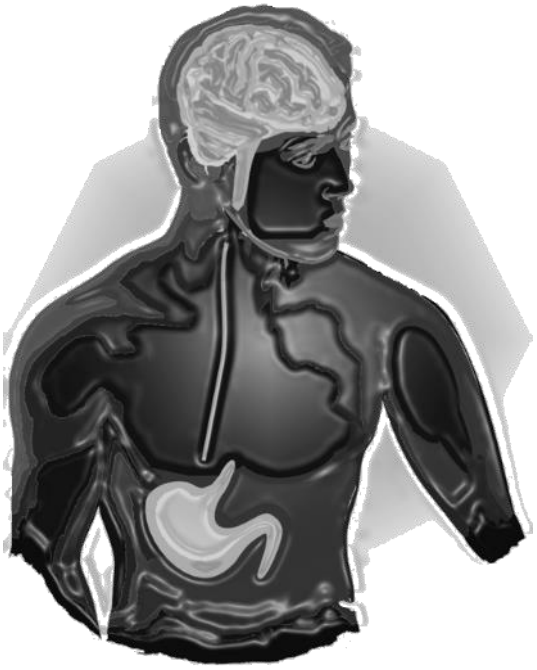

Figure 6: The brain and GI tract communicate.

More chronic changes in psychological state are also of importance in IBS. It is well established that anxiety disorders as well as physical and sexual abuse are causally predictive of IBS and are possibly related to the degree of visceral hypersensitivity[27].

Clinical management

Current clinical management of IBS can be considered a process of trial and error. First of all, it is common for practitioners to emphasise that IBS is a benign condition not increasing the risk of colorectal cancer[28], responding directly to patient fears[29].

Several dietary interventions exist as first-line strategy. One comes from the National Institute for Health and Care Excellence (NICE), advising to eat mindfully at regular times in a peaceful environment, to avoid stimuli such as caffeine and alcohol, to avoid fatty foods, and some more specific products[30]. The FODMAP diet requires exclusion of a large number of products for 4 weeks, with the intention to reintroduce these at a quantity at which the patient retains control over their symptoms. The NICE diet and FODMAP exclusion diet are about equally effective, with adequate symptom relief in around half of patients[31]. Food intolerance tests can also be personalised based on an immune response to food concentrates, although their accuracy remains to be demonstrated[32]. Finally, patients can keep a diary of food intake and symptoms, which can subsequently be analysed for food-symptom associations by a dietitian, or computationally using artificial intelligence[33].

If dietary interventions do not achieve good results, or if the patient deems the dietary guideline too difficult to follow, medications can be prescribed in order to normalise stool form (e.g. the μ-opioid agonist loperamide, the GC-C receptor agonist linaclotide) or to reduce pain (e.g. the opioid receptor modulator eluxadoline, central sensory modulating antidepressants). The efficacy of these medications has been reviewed[34].

Psychotherapy is often used for treatment-refractory patients having moderate to severe IBS, and can be cognitive behavioural therapy[35] or hypnotherapy[36], each of which has rendered good results. An overview is given in figure 7.

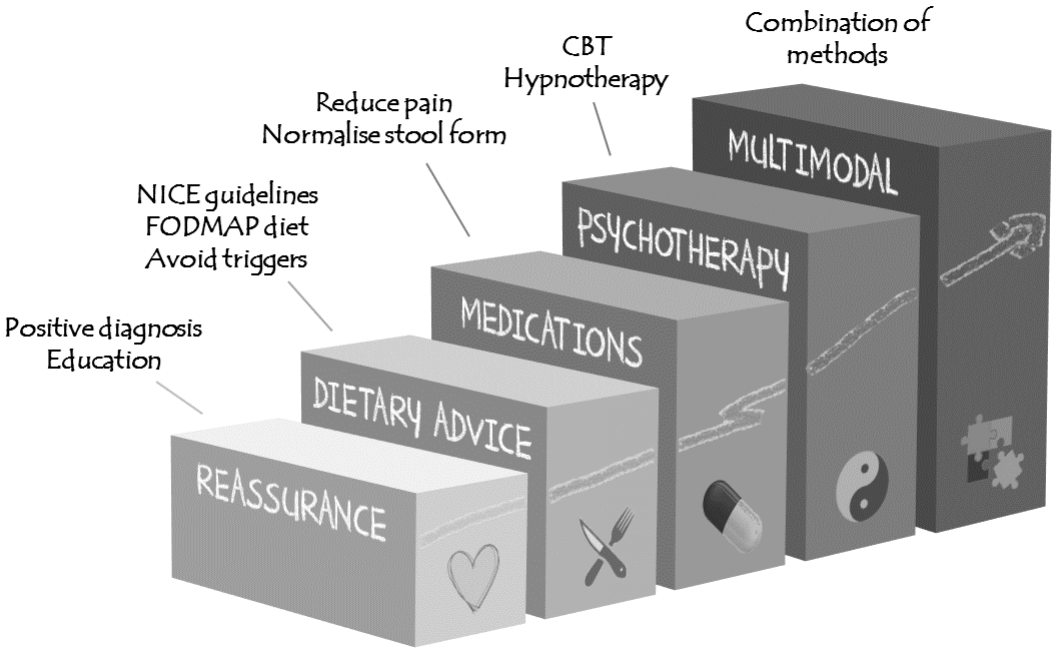

Figure 7: Current clinical management of IBS is a stepwise approach based on symptom severity.

Other treatments include enteric-coated peppermint oil supplements, which demonstrably benefit some patients probably through smooth muscle relaxation[37]; probiotics, which are live bacteria assumed to improve the relative microbial abundance, although their success depends largely on the exact strains that are supplemented[38]; and mast cell stabilisers such as ketotifen, which obviously assumes that this is the pathophysiologic mechanism at play[39]. There is no scientific support for alternative therapies such as acupuncture[40]. Most treatments reach 50% of patients having adequate symptom relief. Although not bad, a large part of this will be a placebo effect[41].

The next two sections will explain why both IBS treatment and IBS research remain suboptimal. Key challenges are complex interactions in pathophysiology and heterogeneity between patients.

Challenge 1: within-person heterogeneity due to complex interactions

A stressor sometimes does, but sometimes does not trigger GI symptoms. Such within-person heterogeneity can confuse the search for symptom triggers and needs to be accounted for in scientific studies[42]. One possible explanation could be that endogenous factors in the GI tract compose a 'latent state of sensitisation', which determines the extent of additional stressors needed to reach a symptomatic state (figure 8). The theory of such a latent state is supported by the synchrony between the female menstrual cycle and GI symptom episodes, for instance, as apparently hormone levels influence the susceptibility to GI symptoms[43].

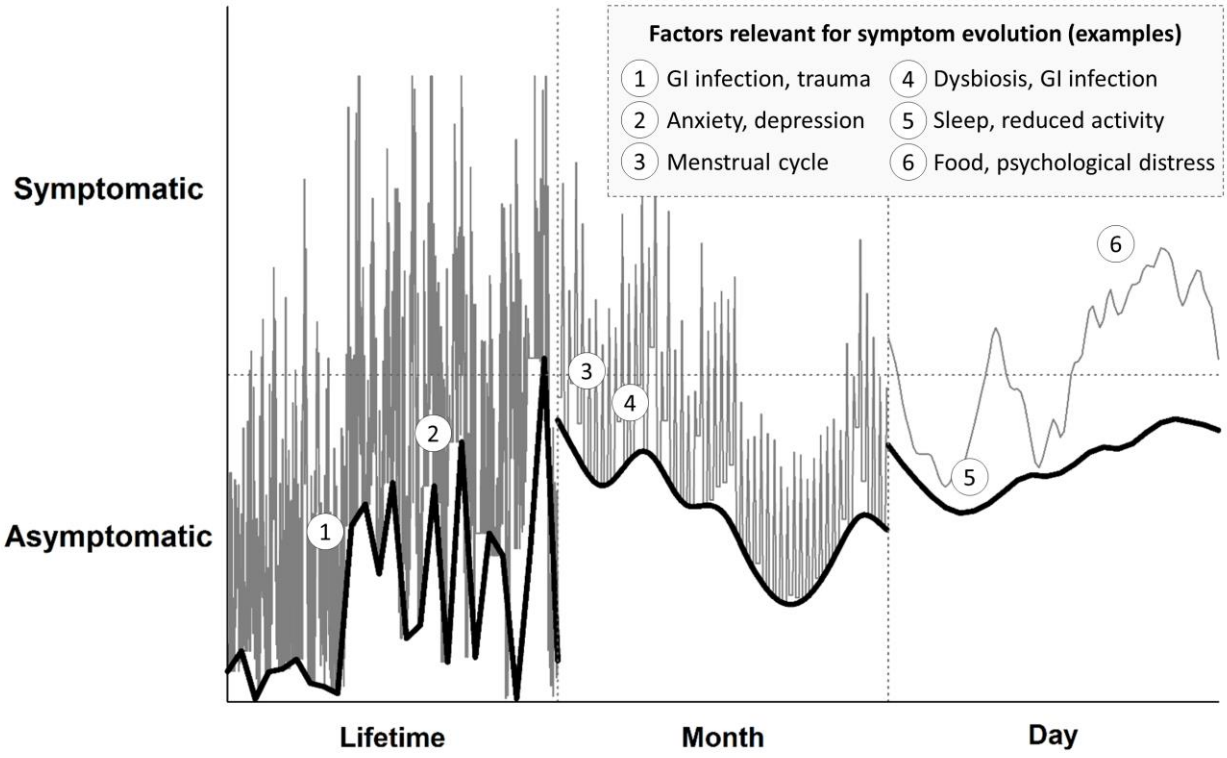

Figure 8: Proposed evolution of GI symptoms and factors influencing this. The thick black line represents a latent state of the GI tract.

While the effect of exogenous factors such as food and psychological distress is short-lived, endogenous factors usually span over a longer term. These include changes to the relative abundance or composition of the microbiota, disruption of the intestinal barrier, activation or altered responses of the local immune system[24], or a change in brain responses[44]. Of course, such physiologic factors themselves are partially influenced by lifestyle, but there is particular importance in the interaction between exogenous and endogenous factors[20] (note that interactions would form extra layers in figure 4, but were not visualised as they are typically uncharacterised and almost infinite in number). Dealing with these complex interactions is a key challenge in IBS research.

Challenge 2: between-person heterogeneity due to different mechanisms

A second challenge for IBS research and treatment is that every patient is unique. Some patients respond well to a dietary intervention. However, for others the diet will be irrelevant for GI symptom generation, and consequently no dietary intervention will have an effect. Figure 9 exemplifies the discrepancy between group-level (left) and individual-level (right) triggers of GI symptoms.

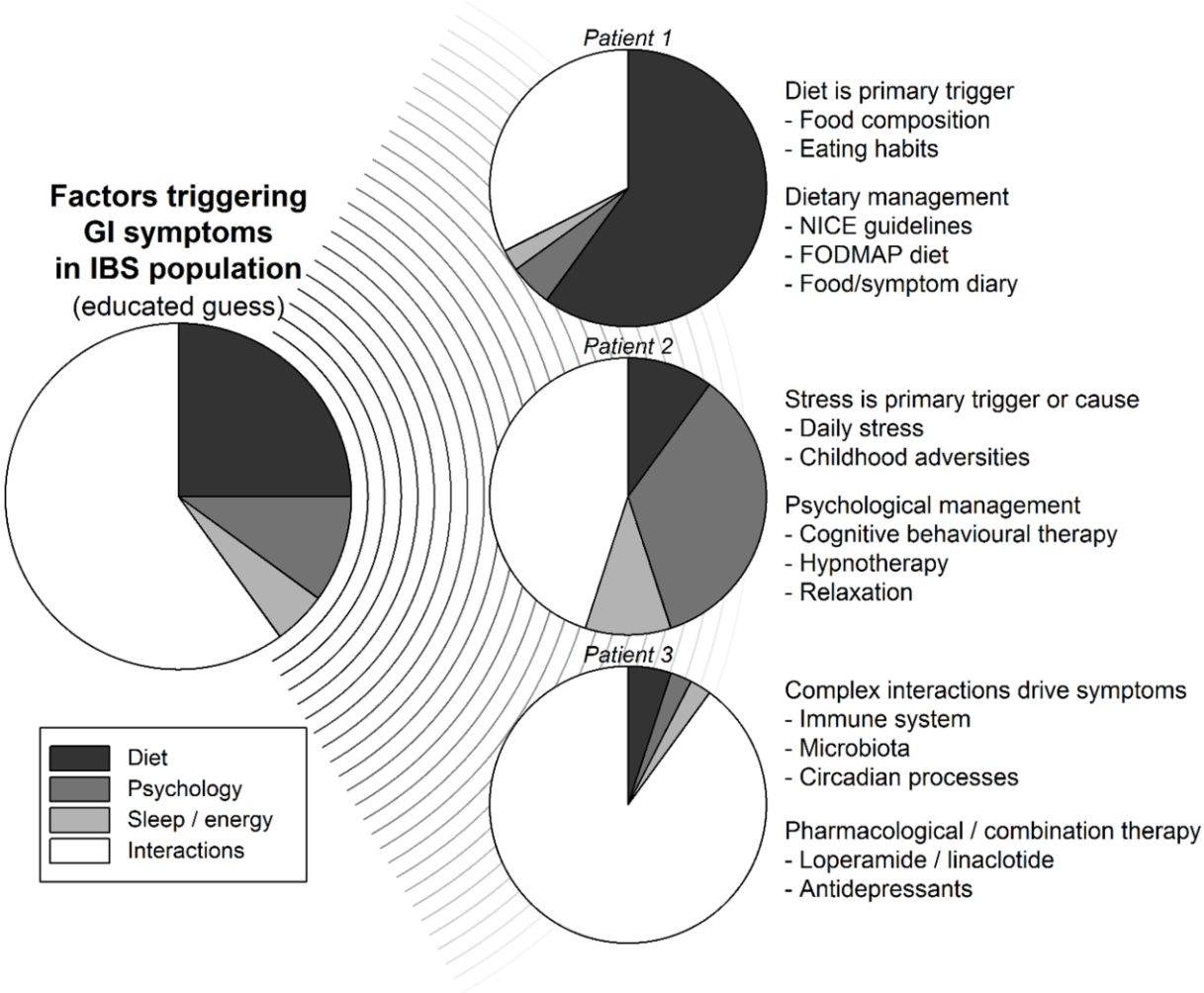

Figure 9: Several factors can cause or trigger GI symptoms (left). However, this will differ from patient to patient (right). Percentages in the pie charts are a guesstimate based on treatment responses to dietary or psychological interventions, as well as within-person correlations between dietary and psychological factors. 'Interactions' correspond with figure 8 below the thick black line.

It has been attempted to define subgroups of IBS patients, each of which would have their own treatment algorithm. Subgroupings may be based on predominant stool form (diarrhoea, constipation, mixed, or neither[45]), the onset of IBS (post-infectious or other[46]), the presence of psychological or somatic symptoms[47], symptom pattern during the day[42], or specific mechanisms (bile acid malabsorption[48], small intestinal bacterial overgrowth[49], fructose intolerance[50]). Despite all of the existing subgroupings, the quest for stratification of IBS remains ongoing.

Aims and studies

This thesis aims to further our understanding of IBS, and provide tools for its clinical management. It does so using 5 studies, which address specific research questions on IBS diagnostics, epidemiology, development, mechanisms, and management:

1. Clevers E, Whitehead WE, Palsson OS, Sperber AD, Törnblom H, Van Oudenhove L, Tack J, Simrén M. Factor Analysis Defines Distinct Upper and Lower Gastrointestinal Symptom Groups Compatible With Rome IV Criteria in a Population-based Study. Clin Gastroenterol Hepatol. 2018 Aug;16(8):1252-1259.
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Study	Aspect	Aim(s)
1	Diagnostics	- To assess the validity of the Rome IV criteria to define IBS.
2	Epidemiology	- To investigate comorbidity patterns of IBS. - To identify health problems that increase the risk of IBS or vice versa.
3	Development	- To characterise the evolution of IBS symptoms over a 5-year period. - To investigate and compare the roles of psychological features in IBS.
4	Mechanisms	- To identify personal food-symptom or stress-symptom associations. - To identify latent classes of daily symptom patterns.
5	Treatment	- To validate the use of food-symptom diaries to give personalised lifestyle advice for managing GI symptoms. - To identify common triggers for GI symptoms.

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Factor analysis defines distinct upper and lower gastrointestinal symptom groupings compatible with Rome IV in a population-based study

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Abstract

Background and aims: The Rome IV criteria define functional gastrointestinal (GI) disorders (FGIDs) by specific symptom combinations. It is possible to empirically evaluate these symptom combinations by factor analysis, but this has not been done for Rome IV, and most factor analyses based on the previous versions of the Rome criteria did not use population-based samples. We therefore investigated symptom groupings on the Rome IV questionnaire using factor analysis in a population-based sample.

Methods: The Rome IV questionnaire was completed online in English by a population-based sample of 5931 respondents from the United Kingdom, United States, and Canada (49% female, age range 18 to 92 years). We performed an exploratory factor analysis on the Rome IV questions. Next, we performed a confirmatory factor analysis to compare the exploratory factor result to that of the Rome IV criteria.

Results: The exploratory factor analysis showed eight factors explaining 45% of the response variance, characterised as constipation, diarrhoea, irritable bowel syndrome (IBS), abdominal pain, heartburn, nausea/vomiting, globus, and other upper GI symptoms. Most factors corresponded to distinct FGIDs defined in Rome IV, exceptions being the factors of abdominal pain and upper GI symptoms. In confirmatory factor analysis, the exploratory model fitted slightly better than that based on the Rome IV criteria (root mean square error of approximation (RMSEA): 0.063 vs. 0.077).

Conclusion: Factor analysis identifies distinct upper and lower gastrointestinal symptom groupings compatible with the Rome IV criteria. Our findings support the use of the Rome IV criteria in research and clinical practice as a basis for diagnostics and management.

Introduction

Functional gastrointestinal (GI) disorders (FGIDs) are syndromes defined by clusters of symptoms emanating from the GI tract, with population prevalences for many of these disorders ranging between 5 and 10%.[1] More than 20 FGIDs are defined by the published Rome IV criteria,[2] based on specific GI symptom combinations.

The distinction of each FGID as a separate entity may be corroborated by investigating how GI symptoms group together in the general population, and whether these symptom groupings are compatible with the Rome criteria. One method of doing so is factor analysis: a statistical procedure that groups variables with strong inter-correlations. Consistent agreement between factor analysis

and the Rome symptom criteria would then suggest that the disorders represent distinct entities which are identified by these symptom criteria. Previous studies have performed factor analyses on GI symptoms, and compared the resulting factors to the structures of the Rome I and II criteria,[3,4] as well as the Manning criteria for irritable bowel syndrome (IBS).[5] For example, Whitehead *et al*[6] found factors of IBS (i.e. abdominal pain related to stool patterns), nausea, constipation (including straining and incomplete evacuation), and a heterogeneous group of other GI symptoms. A similar IBS factor was found by Taub *et al*[7] and Talley *et al*.[8] Whitehead *et al*[9] performed a factor analysis on GI symptoms in gastroenterology clinic patients, and reported thirteen distinct factors, including IBS, constipation, diarrhoea, and anorectal pain, but also several upper GI factors. Finally, Siah *et al*[10] described amongst others a factor of bloating, associated with flatulence and belching. In conclusion, factor analyses can be used to substantiate the definitions of FGIDs.

The above factor analyses assessed Rome I, II, and III diagnostic classifications, but such analyses have not been performed since the publication of Rome IV. Furthermore, most of the previous factor analyses did not use population-based samples. We therefore aimed to empirically substantiate the latest definitions of FGIDs in a large, population-based sample by factor analysis.

Methods

Rome IV survey

We used an internet-based Rome IV survey involving 6300 individuals, with methodology described previously.[1] Briefly, participants were a nationally representative adult population sample from the United States (US), United Kingdom (UK), and Canada, as selected by the survey vendor Qualtrics Inc. Quota-based sampling was used to ensure equal proportion of sex (50:50), age groups (40% aged 18-39, 40% aged 40-64, and 20% aged 65 and older), and education level (30% maximum with more than sixteen years of formal education) across the countries. In the US sample, the survey vendor also selected 20% African Americans and 20% Hispanic ethnicity respondents, but these demographic shifts were not done in the UK or Canada. The survey was presented as a health survey without specific mention of gastroenterology, in order to prevent enrichment of participants with GI problems. All respondents confirmed informed consent online at the start of the survey. To ensure reporting quality, three questions were presented twice, and there were two attention verification questions. The survey was completed by a total of 6300 respondents, i.e. 2100 for the

US, UK, and Canada respectively. Before data collection started, the study was reviewed by the Institutional Review Board (IRB) at the University of North Carolina and deemed IRB-exempt as all study participants were anonymous to the investigators.

Data pre-processing

Of the 6300 respondents, we included those who satisfied both attention verification questions and the response consistency checks with the three repeated symptom questions. This left 5931 respondents in the analysis sample. Of the 86 Rome IV questions, we included those with ordinal response scales, as these can be used to compute correlations. Excluded questions mostly related to the length of time the symptom had been present. No questions critical to a Rome IV FGID diagnosis were excluded. A total of 49 Rome IV questions were included in the analysis.

Exploratory factor analysis

We performed an exploratory factor analysis using the "factanal" function in R version 3.3.3.[11] This is a statistical procedure that groups variables with strong inter-correlations, and as such identifies the key variable groupings. A correlation matrix of the Rome IV questions was computed, and orthogonal factors with an eigenvalue larger than 1 were retained. Factor analysis was performed with maximum likelihood estimation and varimax rotation. Loadings of 0.40 and larger were deemed relevant.

Confirmatory factor analysis

We used confirmatory factor analysis to confirm that Rome IV successfully captures the GI symptoms into distinct FGID entities. This is done by fitting a pre-specified model of the Rome IV structure, and comparing this model to the data-driven structure resulting from the exploratory factor analysis. In case the models are similar of composition and statistical fit, this further reinforces the Rome IV criteria.

The factor structure of the Rome IV criteria was pre-specified as follows (see table 2 for reference). Globus was defined as a lump in the throat occurring between meals (items 1 and 3). Functional heartburn was defined by burning sensations in the chest (items 7 and 9). Functional dysphagia was defined by foods sticking in the oesophagus[12] (items 8 and 12). Postprandial distress syndrome was

defined by postprandial fullness and early satiety (items 14 and 16). Chronic nausea and vomiting syndrome was defined by nausea and vomiting[13] (items 21 and 23). IBS was defined by pain anywhere in the abdomen related to defecation (items 40, 41, 42, and 43). Functional constipation was defined by stools that are hard, infrequent, and hard to pass[14] (items 49, 51, 52, 53, 54, and 55). Biliary pain was defined by pain in the right upper quadrant[15] (items 68, 69, 70, 71, and 72). Other FGIDs were defined by only one eligible Rome IV question, and were not in the confirmatory model in order to be consistent with the exploratory model. The exploratory and Rome IV based models were compared by root mean square error of approximation (RMSEA).

Results

There were 5931 respondents in the analysis sample. The demographics approximated those from recent census reports[16-18] by age and sex categories. The age ranged from 18 to 92 years old and 49% was female (figure 10). Common FGIDs were: functional dyspepsia, postprandial distress syndrome: 7.7%; functional constipation: 6.3%; proctalgia fugax: 5.9%; IBS: 5.7%; functional abdominal bloating/distension: 5.6%; functional diarrhoea: 5.4%.

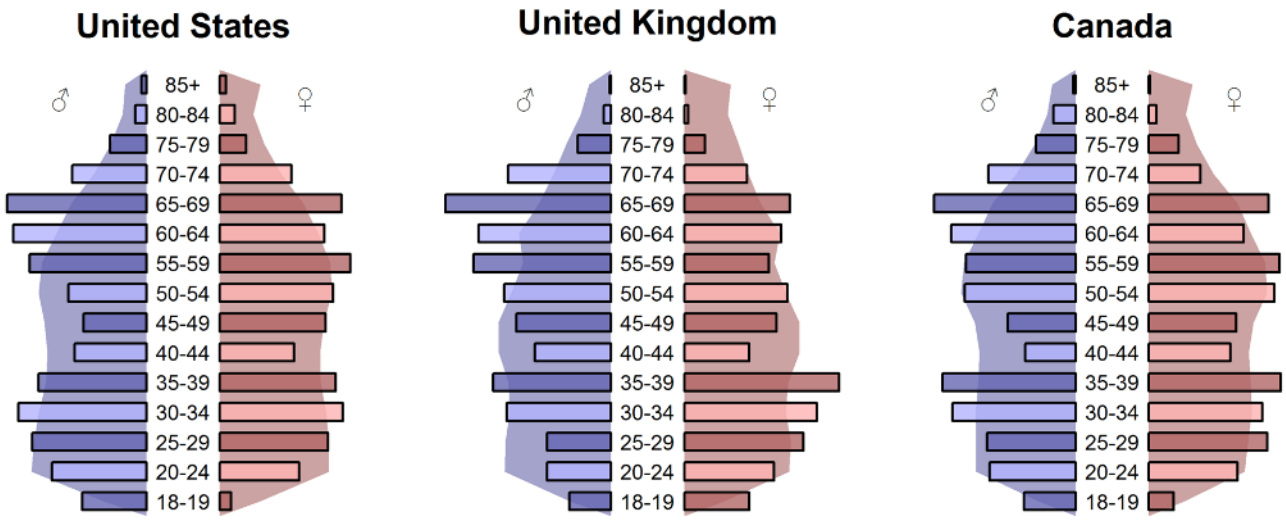

Figure 10: Age and sex of the respondents in the present study (bars) compared to those of recent census reports (shade).

Exploratory factor analysis

Eight distinct factors emerged from the factor analysis, and were characterised as constipation, diarrhoea, IBS, abdominal pain, heartburn, nausea/vomiting, globus, and other upper GI symptoms

(table 2). Taken together, they explained 45% of the response variance. The constipation factor held all items that define functional constipation in Rome IV. Diarrhoea was described by loose stools, including those after a meal, as well as urgency, and was thus compatible with functional diarrhoea in Rome IV. The IBS factor held the Rome IV defining questions for IBS (abdominal pain related to defecation, stool frequency, and stool consistency) with large loadings (r >= 0.73), but also pain in the epigastric or right upper quadrant regions related to defecation, albeit with smaller loadings (r = 0.45 and 0.48). In the factor of abdominal pain, pain was not associated with defecation but did interfere with usual activities, i.e. symptoms partially covering both biliary pain[15] and centrally mediated abdominal pain syndrome in Rome IV.[19] Heartburn and globus overlapped with the Rome IV definitions for functional heartburn and globus. The factor nausea/vomiting contained the items used to define chronic nausea and vomiting syndrome in Rome IV, plus retching and vomiting related to right upper quadrant pain (r = 0.58 and 0.63). Finally, there was a factor of upper GI symptoms, containing two symptoms of functional dyspepsia in Rome IV (epigastric pain and postprandial fullness), but also bloating, belching, abdominal pain, and some oesophageal symptoms. Some items stood in isolation, particularly pain with swallowing, early satiety, abdominal pain related to a meal, faecal incontinence, and anorectal pain (r < 0.40). All items and their rotated factor loadings are shown in table 2. Results separate for the three country samples are available in online supplementary information.

Table 2: Factor loadings after varimax rotation.

Item	Topic	Constipation	Upper GI	Abdominal pain	IBS	Nausea/vomiting	Diarrhoea	Heartburn	Globus
1	Lump in throat	.15	.36	.03	.02	.12	.08	.08	**.78**
3	Lump in throat when not eating	.09	.05	.19	.14	.08	.04	.19	**.48**
4	Pain with swallowing	.12	.17	.23	.08	.22	.03	.30	.07
5	Chest pain	.20	**.49**	.10	-.01	.18	.08	.22	.18
7	Chest pain as burning sensation	.07	.12	.19	.13	.05	.05	**.62**	.07
8	Chest pain and food sticking after swallowing	.09	.10	.08	.12	.18	.05	**.45**	.09
9	Heartburn	.15	**.41**	.07	.05	.11	.12	**.49**	.08
12	Foods stuck in chest	.18	**.43**	.05	.03	.20	.11	.33	.22
14	Postprandial fullness	.18	**.41**	.18	.04	.25	.13	.21	.08
16	Early satiety	.22	.36	.17	.05	.30	.13	.15	.09
18	Epigastric pain/burning	.15	**.55**	.29	.03	.25	.09	.26	.04
19	Epigastric pain/burning improved by defecation	.12	.03	-.05	**.45**	-.02	.00	.21	.10
21	Nausea	.16	.38	.29	.08	**.54**	.11	.11	.07
23	Vomiting	.11	.27	.15	.05	**.66**	.07	.10	.05
25	Self-induced vomiting	.06	.00	-.01	.00	.17	.09	.18	.07
32	Food coming back up after swallowing	.16	**.44**	.07	.08	.37	.12	.21	.12
34	Retching	.14	.14	.16	.07	**.58**	.14	.15	.09

35	Vomiting when food comes back up	.20	.15	.21	.09	.63	.13	.09	.01
37	Food coming back up is recognisable	.04	.10	.11	.12	.18	-.01	.05	.06
38	Belching	.09	.40	.15	.04	.27	.10	.19	.05
40	Pain anywhere in the abdomen	.25	.63	.33	.11	.13	.18	.02	.05
41	Abdominal pain related to defecation	.14	.03	.06	.73	-.01	.13	.03	.01
42	Abdominal pain related to stool consistency	.20	.07	.11	.85	.08	.19	.05	.04
43	Abdominal pain related to stool frequency	.22	.08	.16	.75	.13	.23	.10	.03
45	Abdominal pain related to a meal	.09	.13	.33	.38	.13	.25	.22	.04
46	Abdominal pain limits usual activities	.17	.14	.54	.27	.24	.16	.10	.05
49	Hard stools	.61	.13	.10	.14	.08	-.03	.12	.07
51	Infrequent stools	.55	.08	.18	.08	.14	.03	.04	.06
52	Straining during bowel movements	.80	.16	.09	.18	.08	.04	.11	.06
53	Incomplete bowel emptying	.72	.19	.13	.20	.12	.20	.09	.06
54	Anorectal obstruction / blockage	.81	.20	.14	.14	.10	.10	.09	.06
55	Manual manoeuvres to facilitate defecation	.52	.14	.13	.05	.11	.04	.10	-.01
59	Loose stools	.07	.21	.09	.21	.15	.73	.08	.03
61	Loose stools following a meal	.03	.05	.17	.21	.09	.64	.11	.06
63	Urgency	.20	.25	.18	.20	.12	.64	.10	.03
65	Bloating / abdominal distension	.37	.42	.20	.15	.03	.27	.07	.08
68	Right upper quadrant pain	.25	.63	.38	.09	.14	.17	.01	.03
69	Long-lasting right upper quadrant pain	.18	.18	.71	.08	.12	.09	.10	.07
70	Right upper quadrant pain of steady severe level	.19	.17	.74	.09	.14	.14	.07	.05
71	Right upper quadrant pain at different intervals	-.07	-.12	-.12	.11	-.10	.01	.03	-.02
72	Right upper quadrant pain limits usual activities	.12	.19	.63	.07	.26	.07	.07	.04
73	Right upper quadrant pain related to defecation	.17	.07	.13	.48	.05	.14	.01	.03
74	Right upper quadrant pain related to posture	.10	.02	.08	.13	.09	.06	.15	.00
75	Right upper quadrant pain improved by medicine	.05	.08	.04	.01	.05	.05	.42	-.01
76	Right upper quadrant pain related to vomiting	.11	.16	.37	.05	.57	.10	.17	.04
77	Right upper quadrant pain related to back pain	.18	.21	.40	.07	.14	.07	.17	.05
78	Right upper quadrant pain waking one up	.13	.25	.51	.04	.26	.15	.15	.00
80	Faecal incontinence	.11	.28	.07	.09	.13	.36	.05	.01
83	Anorectal pain	.38	.38	.13	.12	.11	.17	.02	.04

Of the 5931 respondents, 62% met the Rome IV symptom threshold for at least one single symptom that is part of the definition of FGIDs (figure 11). Symptoms were sometimes confined to one factor (19%), but often covered items from two (11%) or more (32%), indicating a degree of overlap between the various GI symptoms. The most common symptom was abdominal pain related to defecation (21%) followed by bloating/abdominal distension and loose stools (19% each), whereas no oesophageal or gastroduodenal symptom was particularly common (maximum 10%).

As can be appreciated in figure 11, the IBS factor had the strongest within-factor loadings and correlations: of the 30% who met the Rome IV symptom threshold for at least one of the items in the IBS factor, 77% met the criteria for at least two items (note the contrasting black and white colour patterns for IBS in figure 11). By contrast, of the 33% who met the Rome IV symptom threshold for at least one upper GI item, only 51% met the criteria for at least two. Many upper GI items thus stood in isolation, possibly because many upper GI FGIDs are based on a single key symptom rather than a combination of symptoms, unlike most functional bowel disorders.

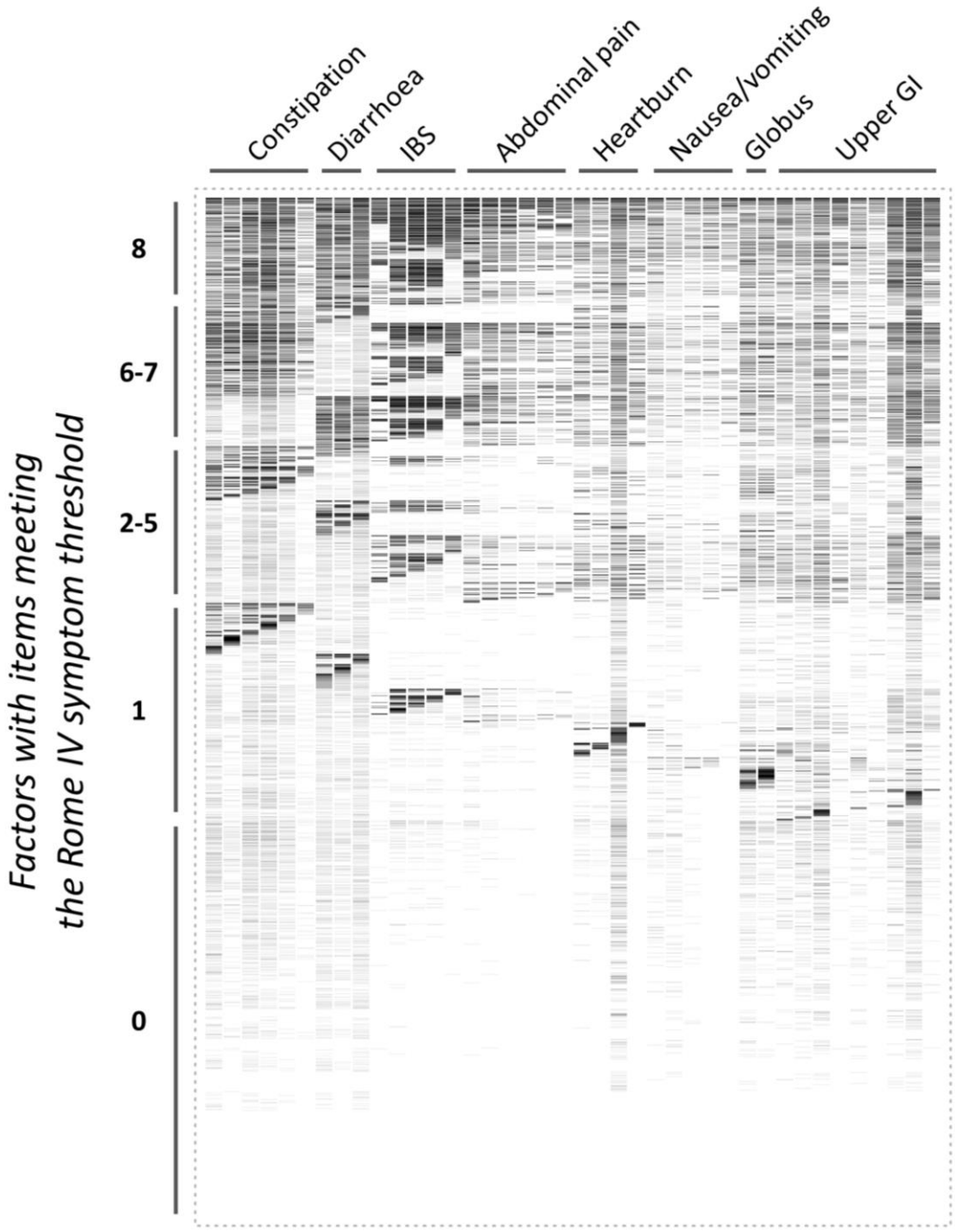

Figure 11: Raw data. Columns are Rome IV questions sorted numerically by factor. Rows are respondents, sorted by the number of factors with items meeting the Rome IV symptom threshold. Darker colours represent higher (worse) responses.

Confirmatory factor analysis

The exploratory factor model had a slightly better fit than that of the Rome IV model (RMSEA: 0.063 vs. 0.077, chi-square: 17500 vs. 8932, df: 712 vs. 247). However, the difference in fit was small, also given that the most factors and FGIDs were represented in both the exploratory and Rome IV model, with near-identical compositions (figure 12). As can be seen in figure 12, the confirmatory model had coefficients of a magnitude comparable to those of the exploratory model (these are the values

on the diagonal lines: compare left versus right). One item had a negative coefficient in the confirmatory model: right upper quadrant pain at different intervals (item 71, -0.16, figure 12), indicating that it did not match well with the factor for biliary pain as hypothesised based on Rome IV.

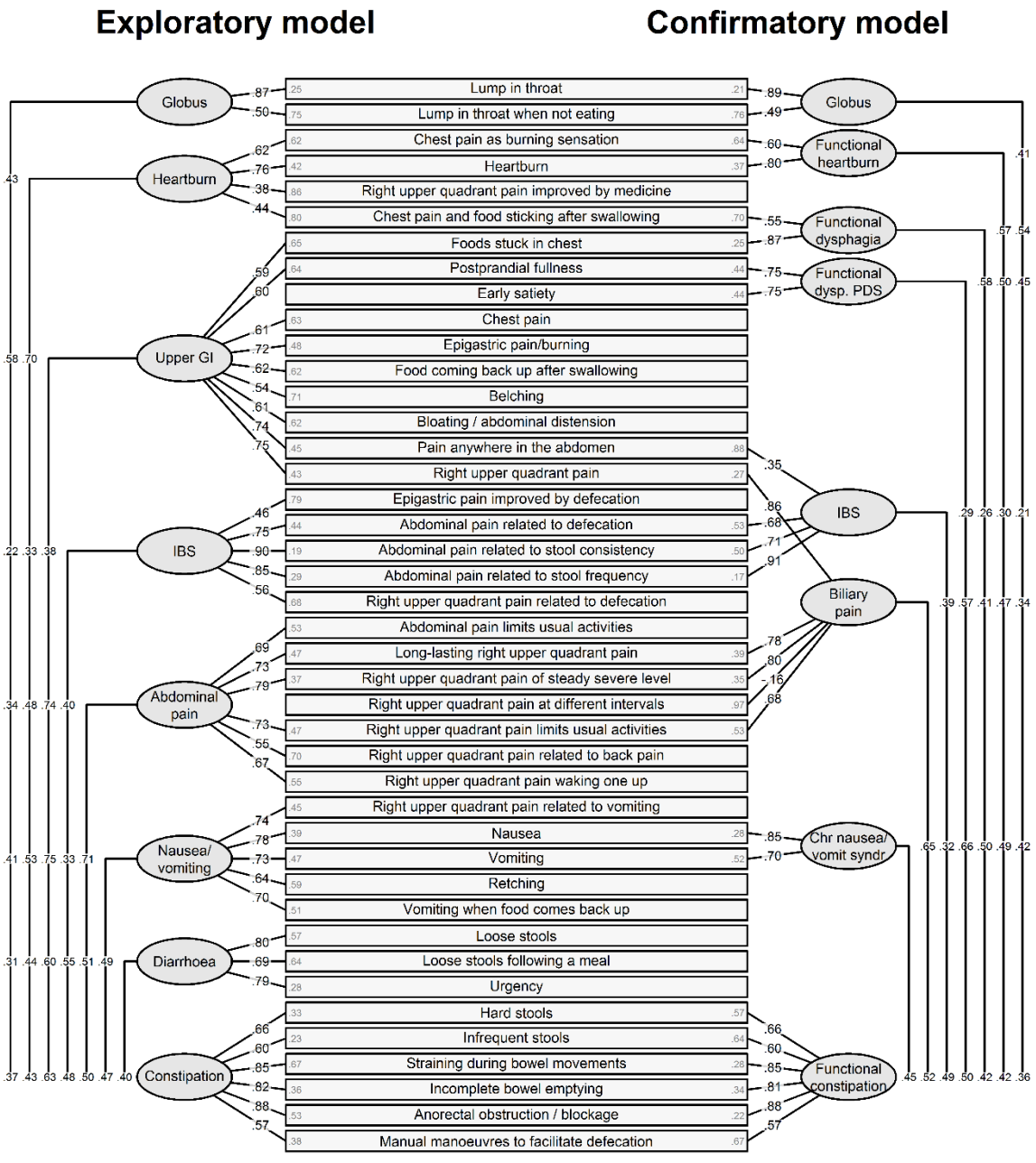

Figure 12: Schematic overview of the exploratory (left) and confirmatory (right) factor models. Ovals are factors, rectangles are Rome IV items. Values on diagonal lines are standardised coefficients (factor loadings), and indicate how strongly each item loads on the factor that it defines. Values on vertical lines denote covariances of factors. Values in boxes are error terms.

Discussion

The present study empirically evaluated the symptom combinations in the Rome IV criteria, and found eight distinct symptom groupings, these being constipation, diarrhoea, IBS, abdominal pain, heartburn, nausea/vomiting, globus, and other upper GI symptoms. All in all these corresponded well with the Rome IV structure.[2]

The factors for IBS, constipation, diarrhoea, globus, heartburn, and nausea/vomiting closely matched the Rome IV criteria for IBS, functional constipation, functional diarrhoea,[14] globus, functional heartburn,[12] and chronic nausea and vomiting syndrome[13] respectively, thereby reinforcing the Rome IV criteria for these FGIDs. Moreover, these factors were quite similar to those reported in factor analyses of earlier Rome editions.[6-10] The IBS factor was the most distinct, with respondents scoring either very high or very low on all defining questions. While constipation and diarrhoea are often seen in IBS patients, IBS is a heterogeneous condition, and as such it is not unexpected to see factors for the core element of IBS (pain related to stool patterns) as well as for the separate stool patterns.

We found a separate factor for abdominal pain, i.e. of a different nature than IBS, which also has been described in earlier studies.[9] It covered both items from biliary pain (right upper quadrant pain)[15] and centrally mediated abdominal pain syndrome (pain restricting usual activities).[19] This factor does not cleanly represent biliary pain, as the item of the pain taking place at different intervals loaded negatively on this factor, while being a defining item in Rome IV. Instead it may represent centrally mediated abdominal pain syndrome, in which the pain is nearly continuously present. Nevertheless, it is difficult for respondents to sense exactly where the pain is located (possibly due to diffuse activation of nociceptive systems in visceral organs),[20] explaining the overlap between pains in the various abdominal sub-regions. Moreover, irrespective of factor structure, it is possible that symptoms overlap between different disorders due to common pathophysiological mechanisms.

Upper GI symptoms factored into heartburn, globus, and nausea/vomiting. There was also a factor with a combination of upper GI symptoms including functional dyspepsia and overlapping symptoms such as belching and bloating, which was also found by Siah *et al*.[10] Whitehead *et al*[9] reported separate factors of heartburn, dysphagia, globus, rumination syndrome, and dyspepsia, capturing the structure proposed in Rome I. Others saw factors of nausea and gas/belching/acid[6,7] or reflux.[8] Factor analyses have also been performed on different questionnaires, such as the reflux disease questionnaire, where factors were found for regurgitation (e.g. acid taste), heartburn, and

dyspepsia, although upper GI symptoms overlapped considerably,[21] in line with the present study. Siah *et al*[10] further discussed a meal-related factor. Meal-related abdominal pain in the present study did not load on any factor, with the largest loadings being for IBS (r = 0.38) and abdominal pain (r = 0.33). The existence of a broad factor of upper GI symptoms may imply a degree of common pathophysiology between these items. Common mechanisms may be peripheral or central. For example, Fischler *et al*[22] found a factor of bloating and postprandial fullness to be associated with delayed gastric emptying, a factor of belching associated with gastric hypersensitivity, and a factor of epigastric pain associated with both gastric hypersensitivity and several psychosocial factors. In summary, the factor structure of upper GI symptoms found in the present study is quite consistent with those of prior studies, and partially reinforces the Rome IV criteria, although some upper GI symptoms were difficult to separate out using the Rome IV questionnaire.

Finally, confirmatory factor analysis showed that Rome IV groups symptoms in a manner that captures the variance in the population, close to the factors found through computerised means (i.e. the exploratory factor analysis). The item "right upper quadrant pain at different intervals", defining biliary pain in Rome IV, was the only odd one out to have a negative coefficient for this FGID. It may be considered to rephrase this item in future Rome editions.

Our study has two strengths. First, while factor analytical studies have contributed to amendments of Rome I, we present a factor analysis for the published Rome IV questionnaire. The results reinforce the Rome IV criteria, which can be used in research and clinical care for diagnostics and specific management of FGID patients. Second, we did so in a large sample in three countries, with demographics close to those of the general population. Generalisability of our findings to the population should therefore be high. It remains to be seen whether other languages, countries, or continents (e.g. Asia) would render similar findings,[23] although the recent factor analysis by Siah *et al*[10] of Rome III shows that any differences are likely to be subtle. A limitation is the absence of information on how many potential respondents chose to ignore the invitation to partake in the survey, despite the close similarity between sample and population demographics. Furthermore, some FGIDs are described by only one key symptom in Rome IV, so that these will not be supported by factor analysis. However, it is useful to include these symptoms into the exploratory analysis to determine whether there are unpredicted symptom associations that should be recognised.

To conclude, upper and lower GI symptom groupings compatible with Rome IV diagnoses exist in the general population, and can be identified using the English Rome IV questionnaire in a large population-based sample from three English-speaking countries. Our results provide further basis

for practising clinicians to use the Rome IV criteria throughout the process going from symptoms to diagnosis and management. While our results reinforce the Rome IV criteria, some upper GI symptoms were difficult to separate out, and more work is needed to reach a distinct classification.

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Health problems associated with irritable bowel syndrome: analysis of a primary care registry

Comorbidity profile of IBS in primary care

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Summary

Background: Associations between irritable bowel syndrome and other health problems have been described, but comprehensive reports are missing, especially in primary care.

Aims: We investigated which health problems are associated with irritable bowel syndrome, how they cluster together, and when they are typically diagnosed relative to irritable bowel syndrome.

Methods: We used Intego, a general practice registry in Flanders, Belgium. Patients with an irritable bowel syndrome diagnosis (n=13,701) were matched with controls without gastrointestinal diagnosis and controls with organic gastrointestinal disease. Long-term prevalences of 680 symptoms and diagnoses were compared between patients and controls. Results were summarised using functional enrichment analysis and visualised in a network, and we calculated incidence rate ratios in the ten years before and after the irritable bowel syndrome diagnosis for the network's key components.

Results: Various symptoms and infections, but not neoplasms, were enriched in irritable bowel syndrome patients compared to both control groups. We characterised the comorbidities of irritable bowel syndrome as psychosocial health problems, urogenital symptoms and infections, musculoskeletal symptoms, and other somatic symptoms. These had a uniform incidence in the years around the irritable bowel syndrome diagnosis, and did not structurally precede or follow irritable bowel syndrome.

Conclusions: Irritable bowel syndrome shares long-term associations with psychosocial health problems, urogenital symptoms and infections, musculoskeletal symptoms, and other somatic symptoms in primary care. Clinicians are encouraged to take comorbidities into account when diagnosing and managing irritable bowel syndrome, as this may have important treatment implications.

Introduction

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction, defined by recurrent abdominal pain associated with alterations in bowel habits.[1] Its population prevalence is roughly 10%.[2]

IBS is thought to result from the complex interaction between biological factors (e.g. increased intestinal permeability, central sensitisation), psychological factors (e.g. anxiety), and social factors (e.g. early adverse life events, lack of social support), thus generating a biopsychosocial disease model.[3] In line with this conceptualisation, IBS is associated with various biological, psychological, and social health problems, including fibromyalgia,[4] anxiety and depressive disorders,[5] and sexual or physical abuse.[6] Whitehead *et al*[7] compared the prevalence of 76 health problems between IBS patients and matched non-IBS controls. They found various infections to be more common in IBS, including cystitis, urethritis, prostatitis, and respiratory infections, but also stroke. The authors proposed that IBS patients are hypervigilant in detecting somatic symptoms and may have a lower threshold for consulting physicians, a phenomenon not seen in inflammatory bowel disease.[7] Finally, comorbid health problems may arise before, with, or after IBS, which may shed some light on their role in IBS aetiology. One study reported that in individuals without IBS at baseline, anxiety levels predicted IBS onset after twelve years, while in individuals without anxiety at baseline IBS predicted an increase in anxiety.[8] Others found anxiety,[9-11] poor quality of sleep, illness behaviour,[12] and dyspepsia[13] to often develop before IBS. Taken together, studies on the comorbidities of IBS can aid the interpretation of health problems in respect of shared aetiologies with IBS and symptom reporting tendencies.

Most studies, however, highlighted single health problems in association with IBS, or used a baseline to follow-up design. As such, it is difficult to assess whether these health problems should be regarded as separate entities that share predisposing factors with IBS, whether IBS patients have a generalised increase in symptom perception,[7] whether IBS should be considered a systemic disease in which health problems may arise in multiple organs, or whether IBS comorbidity patterns differ across patient subgroups[14]. There is thus a need to place the single comorbidities of IBS into an integrative perspective, and understand when they occur relative to an IBS diagnosis.

Therefore, the present study has three complementary aims, which are addressed in a primary care registry in Belgium. First, we aim to identify which health problems are associated with IBS. Second, we investigate how health problems cluster together within an integrative IBS comorbidity network (hereinafter: "diseasome"). Third, we investigate the incidence of health problems in the years before and after the IBS diagnosis. We hypothesise that a broad range of biological, psychological,

and social problems are more common (i.e. enriched) in IBS compared to control groups, without formulating hypotheses on comorbidity with specific disorders.

Methods

Primary care registry

We used the primary care registry Intego[15] in Flanders, Belgium, as described elsewhere.[16] Briefly, general practitioners (GPs) used the software MediDoc[17] to enter patient diagnoses, including diagnoses made by specialists entered by the GP after hospitalisation. The registry covered the period 1999 through 2015, although diagnostic data prior to 1999 was also taken into account. Diagnoses were from a thesaurus of approximately 65,000 terms, which were computationally restructured to 680 unique International Classification of Primary Care (ICPC) diagnoses (i.e. ICPC-2[18]). Each ICPC diagnosis has a code that specifies the organ system by one letter (e.g. *D* is for digestive system), and the type of diagnosis by a number (codes below 30 are symptom-based diagnoses, hereinafter: "symptoms", and codes above 70 are disorder-based diagnoses, i.e. subdivided into infections, neoplasms, and other diagnoses). Other recorded variables were: GP practice identifier (ID), patient ID, sex, year of birth, year of diagnosis, and the years of the first and last contact with the GP. To ensure data quality and consistency, we only included the data of GP practices with an optimal registration performance, as defined by an average of more than one diagnosis per patient per year, a percentage of diagnoses recorded without using keywords of less than five percent, and consistent parameters over at least three years.[16] In total, 79 GP practices were included, recording 4,254,325 ICPC diagnoses for 319,068 unique patients. Key terms used throughout this paper are defined in table 3.

Table 3: Definitions of key terms used throughout this manuscript. ICPC: International Classification of Primary Care. IBS: irritable bowel syndrome. GI: gastrointestinal.

Term	Definition in the present study
ICPC diagnosis	A categorisation[18] of diagnoses entered by general practitioners. These cover medical health problems, but also symptoms, social health, and health concerns.
Diagnostic category	ICPC diagnoses of a common type or organ. Defined by the letter in the ICPC code.
Enriched	Of a diagnostic category: more prevalent in IBS patients than in controls, more consistently so than other diagnostic categories.

Contact	Moment of consulting the electronic file of a patient. A diagnosis need not be made.
Contact period	Period from the first to the last contact of a patient.
Data period	Period from the first to the last record of a patient (i.e. including historical data).
GI diagnoses	GI diagnoses beyond single symptoms/complaints. Examples are IBS, GI infections, neoplasms, and injuries (ICPC codes: *D70*, *72-81*, *84-99*).
Organic GI diseases	GI diseases with a defined pathology, such as neoplasms, ulcers, and chronic enteritis (ICPC codes *D72*, *74-77*, *81*, *85-86*, *88*, *94-95*). IBS cases were excluded from this group.
"Diseasome"	A network showing all health problems that are common in IBS, and how these are associated with each other.

Aim 1. Health problems associated with IBS

Selection of patients and ICPC diagnoses

Of the 319,068 unique patients, we included those with a data period of at least 10 years in order to reduce the number of false negative IBS cases. The cut-off of 10 years was chosen because, thenceforth, IBS prevalence was stable at 9%, which is in agreement with epidemiological studies.[2] This resulted in a sample of 151,496 patients, 13,701 of whom had at least one IBS diagnosis (ICPC code *D93*) in their electronic medical file. These 13,701 IBS patients were matched with two control groups: patients without a GI diagnosis and patients with an organic GI disease but no additional IBS (defined in table 3). Matching was performed at a 1:1 ratio, by sex and GP practice ID (strict), age at the first record, first contact year, and last contact year, and the length of the contact period and data period (all allowing 25% difference). The 25% difference allowance was chosen to be able to match most IBS patients, although some could not be matched due to the totality of matching criteria. The final analysis included 11,244 and 7,808 patients for the control groups without GI diagnosis and with organic GI disease, respectively.

Of the 680 unique ICPC diagnoses, we included the ones with at least 20 cases in the matched patient groups, because, when calculating risk ratios, divisions by low numbers can lead to extreme values. We also excluded GI diagnoses (ICPC codes *D01-99*) to avoid circular reasoning, leaving 418 and 434 ICPC diagnoses in the analyses for the two control groups (the prevalence of GI diagnoses is shown in online supporting information 2 table S3).

Data analysis

For IBS patients and controls, we extracted the long-term prevalence of each ICPC diagnosis. Long-term prevalence is defined as the prevalence over the period of which we have data (hence not lifetime-prevalence), which is at least ten years per patient. Risk ratios were computed. We did not test for statistical significance of risk ratios for two reasons: first, statistical significance is almost guaranteed given the large sample size; second, risk ratios will not be reproducible and are subject to various biases, including a dissimilar frequency of GP consultation when comparing a group with a positive diagnosis to a group without that diagnosis. To overcome such limitations, we applied a technique commonly used in genetics: functional enrichment analysis.[19] This technique summarises the rank-order pattern of risk ratios, and as such is a single statistical procedure rather than multiple hypothesis tests. The formulae and details of this technique are explained elsewhere[19] (see also figure 14). The technique was performed for all diagnostic categories (n=16, i.e. by the letter of the ICPC codes), and for the subdivisions per category, i.e. symptoms, infections, neoplasms, and other diagnoses (n~64, i.e. four sets for each category).

Aim 2. Interactions of health problems within the "diseasome" of IBS

Selection of patients and ICPC diagnoses

ICPC diagnoses were included based on their association with IBS, i.e. top tertile of risk ratios in aim 1 and long-term prevalence of at least 5% in IBS patients. A total of 28 ICPC diagnoses fulfilled these criteria. Another 118 ICPC diagnoses were in the top tertile of risk ratios in aim 1, but had a prevalence under 5%. These were condensed to 18 newly created diagnostic pools (table 4). In addition, we added diarrhoea and constipation (codes *D11* and *D12*) to understand how comorbidity differs between IBS patients with different stool patterns. There were thus 48 ICPC diagnoses or pools in the analysis.

Table 4: Pooled International Classification of Primary Care (ICPC) diagnoses. Codes are annotated in reference 18.

Construct	Included ICPC diagnoses	Construct	Included ICPC diagnoses
Fear of disease	*A-C, F-Y*: *23-27* (fear of disease)	Urinary infections	*U: 70*, *72*
Heart symptoms	*K: 01-02*, *04-05*	Menstruation symptoms	*X: 02-03*, *05-10*
Arm/hand symptoms	*L: 09*, *11-12*	Genital symptoms female	*X: 01*, *04*, *14-17*
Hip/leg/foot symptoms	*L: 13-17*	Breast symptoms female	*X: 18*, *20-21*
Muscle pain/symptoms	*L: 18-19*	Genital infections female	*X: 70-71*, *73-74*, *90-92*
Involuntary movements	*N: 04*, *07-08*	Genital symptoms male	*Y: 01-02*, *04-06*, *29*
Psychological disorders	*P: 71*, *77*, *79-80*, *82*, *86*	Genital infections male	*Y: 72-76*
Respiratory symptoms	*R: 02-04*, *06-09*	Relationship problems	*Z: 12-13*, *16*, *20-21*, *24*
Urination symptoms	*U: 01-02*, *05*	Health issue other person	*Z: 14-15*, *18-19*, *22-23*

This analysis started from the 13,701 IBS patients with a data period of at least 10 years (aim 1). For each of the 46 ICPC diagnoses, say "X", we matched IBS patients having X with IBS patients not having X by the same criteria as in aim 1.

Data analysis

We performed a so-called network analysis to summarise the comorbidities of IBS in one integrative perspective, and to investigate how they should be interpreted. Briefly, we computed risk ratios as in aim 1 for all 46 ICPC diagnoses. The resulting risk ratio matrix was log-transformed to obtain a weights matrix. Risk ratios based on fewer than 20 cases were converted to missing, and in such cases we imputed the mean of the weights matrix, because network analysis is not compatible with missing values. The R-package *qgraph*[20] was used to create a weighted network of 46 ICPC diagnoses using the Fruchterman-Reingold algorithm.[21] Finally, we highlighted subnetworks of ICPC diagnoses based on clinical/conceptual grounds.

Aim 3. Incidence of health problems in the years around an IBS diagnosis

Selection of patients and ICPC diagnoses

Of the 319,068 unique patients, 17,301 had an IBS diagnosis. Patients having an IBS diagnosis before the contact period were excluded because the density of diagnostic data was far lower before 1999. This resulted in a sample of 10,861 IBS patients, who were matched with controls, although the matching approach was different from that of aim 1 as far more data is required to obtain reliable values for incidence than for prevalence. The following is a summation of differences in matching

strategy between aims 1 and 3. First, a ten-year data period was not necessary for IBS patients as the data period plays no role in an analysis of single years, but did apply to controls to prevent false negative IBS cases. Second, controls were non-IBS rather than patients without a GI diagnosis in order to maximise the sample size. Third, matching was at a 1:3 ratio, as optimum of sample size and reliability. Fourth, matching was also strict for age, as here we obtain values for single years rather than the long term. Fifth, we only included contact data within ten years before or after the first IBS diagnosis, or, for non-IBS controls, the ten years before or after the year in which their respective IBS match had their IBS diagnosis. Sixth, ICPC diagnoses were pooled using the subnetworks from aim 2 in order to increase power, and we also included GI infection (codes *D70* and *D73*) and GI neoplasms (codes *D74* through *D78*). We included 8,779 and 26,337 IBS patients and controls, covering 89,379 and 268,137 person-years respectively.

Data analysis

For both IBS patients and non-IBS controls, we computed incidence rates per ICPC diagnosis for -10 to +10 years relative to the year of IBS diagnosis, at 95% confidence using the R-package *epitools*.[22] The years -10 to -8, -7 to -6, +6 to +7, and +8 to +10 were pooled to improve statistical confidence. For GI neoplasms, we pooled the years -10 to -1 and +1 to +10, and excluded year 0 for reasons of power and bias (there are reports of diagnostic confusion due to overlapping symptoms between IBS and GI neoplasms[23]). Incidence rates were divided by the total number of non-GI diagnoses made for the respective group per time point, in order to obtain information about the reasons for GP contacts, rather than the mere frequency hereof. The analysis thus controls for differences in GP consultation tendencies between IBS patients and controls. Finally, adjusted incidence rates of IBS patients and non-IBS controls were divided, thereby retrieving adjusted incidence rate ratios at 95% confidence. An adjusted incidence rate ratio above 1.0 thus indicates a high incidence in IBS patients compared to non-IBS controls, not explained by a generalised increase in ICPC diagnoses.

Results

Primary care registry

IBS was diagnosed in 17,301 at a median age of 39, whereas organic GI disease was diagnosed in 24,615 at a median age of 45. Two-thirds of IBS patients were women. The median number of

unique ICPC diagnoses per person was 42, 18, and 34 for IBS patients, patients without GI diagnosis, and patients with organic GI disease respectively, of which 25% were symptoms (ICPC codes <30) and 75% were infections, neoplasms, or other diagnoses (ICPC codes >70). Incidence figures are provided in figure 13.

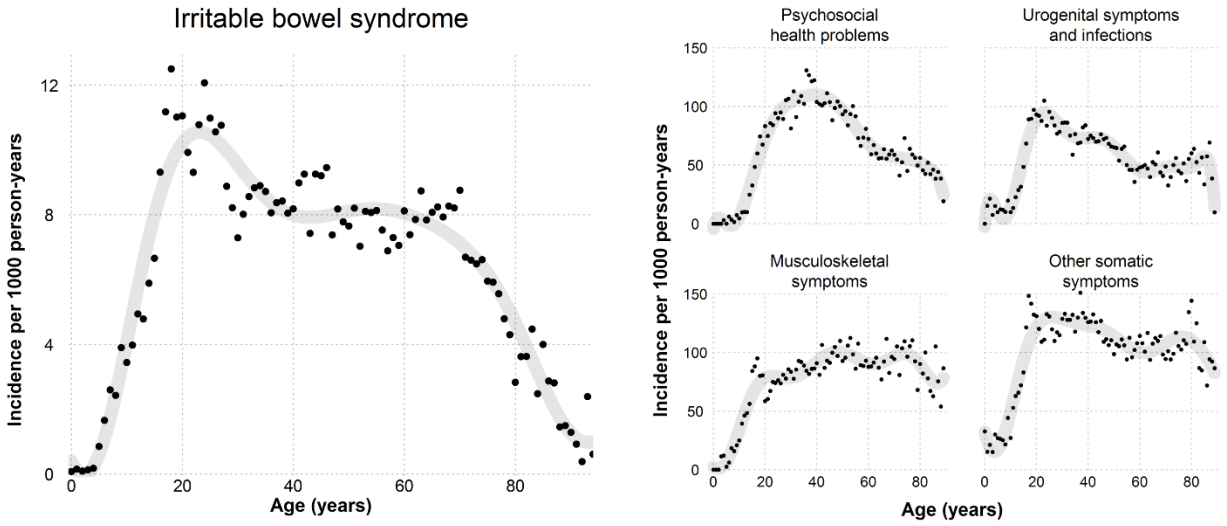


Figure 13: Incidence figures of IBS in the study population (left) and the four clusters of health problems in the IBS⁺ population (right). Shaded lines are fitted polynomials showing the trend.

Aim 1. Health problems associated with IBS

IBS patients had a higher prevalence of 98% of ICPC diagnoses compared to controls without GI diagnosis, with a median and interquartile range of risk ratios of 1.80 [1.48; 2.34]. IBS patients had a higher prevalence of 79% of ICPC diagnoses compared to controls with organic GI disease, with a median and interquartile range of risk ratios of 1.15 [1.03; 1.32]. The risk ratio for somatisation disorder (ICPC code: *P75*) ranked in the top-10 when comparing IBS patients to both controls without GI diagnosis (4.45) and with organic GI disease (2.24). The risk ratio for pregnancy (ICPC code: *W78*), a possible indicator of technical bias as pregnancy should neither be medically related to IBS nor be subject to personal GP consultation tendencies,[24] was modestly increased when comparing IBS patients to controls without GI diagnosis (1.45), but not controls with organic GI disease (1.02). An overview of risk ratios is given in online supporting information 2 table S2.

The following diagnostic categories were enriched as a whole in IBS patients compared to controls without GI diagnosis: psychological (*P*, p<0.001), female genital (*X*, p=0.02), male genital (*Y*, p=0.05), and social (*Z*, p=0.02). In addition, symptoms were enriched for the categories musculoskeletal (*L*,

p<0.001), respiratory (*R*, p=0.001), general (*A*, p=0.007), urological (*U*, p=0.03), and cardiovascular (*K*, p=0.04). Female and male genital infections were enriched (p<0.05), but not neoplasms in any category. When comparing IBS patients to controls with organic GI disease, enrichment patterns were similar but differences were weaker. Results are listed in table 5.

Table 5: Diagnostic categories enriched in irritable bowel syndrome (IBS) patients compared to two control groups. GI: gastrointestinal.

		IBS / no GI diagnosis					**IBS / organic GI disease**				
		Total	Symptoms	Infections	Neoplasms	Other	Total	Symptoms	Infections	Neoplasms	Other
A	General		**					*			
B	Blood/immune										
F	Eye										
H	Ear										
K	Cardiovascular		*								
L	Musculoskeletal		***					***			
N	Neurological						°				
P	Psychological	***	*			*	**				***
R	Respiratory		**								
S	Skin		°					*			
T	Endocrine/metabolic										
U	Urological		*					°			
W	Pregnancy										
X	Female genital	*	***	*			°				
Y	Male genital	*		*		°	*	*	*		
Z	Social	*	*								

***: p<0.001, **: p<0.01, *: p<0.05, °: p<0.10.

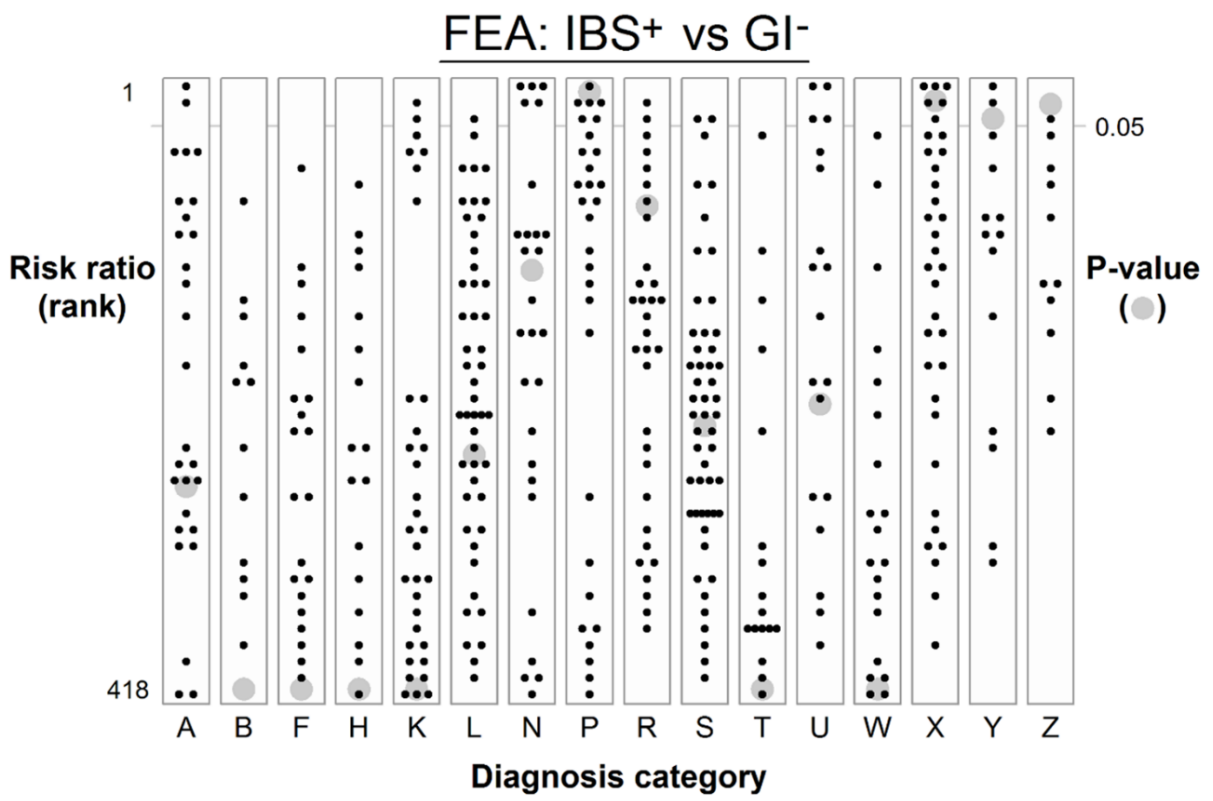
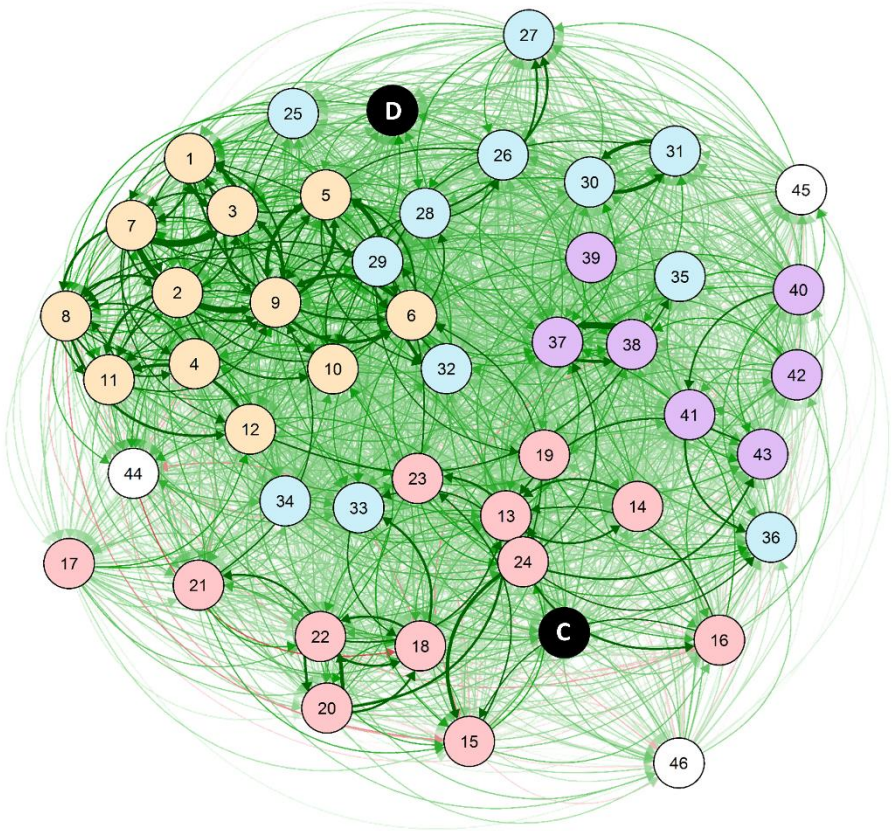


Figure 14: Example of functional enrichment analysis (FEA). Every dot represents an ICPC diagnosis.

Aim 2. Interactions of health problems within the "diseasome" of IBS

The "diseasome" of IBS held 46 ICPC diagnoses, and captured the enrichment results from aim 1. The psychological and social ICPC diagnoses formed a subnetwork, together with fear of disease ("*psychosocial health problems*"). Female and male genital symptoms and infections formed a second subnetwork together with urological symptoms and infections ("*urogenital symptoms and infections*"). Musculoskeletal symptoms formed a third subnetwork ("*musculoskeletal symptoms*"). Different types of symptoms remained, such as general, respiratory, cardiovascular, neurological, and skin symptoms ("*other somatic symptoms*"), alongside concussion, peripheral neuritis/neuropathy, and haemorrhoids. The median RRs within the subnetworks were 1.7, 1.4, 1.5, and 1.3 respectively, and that between subnetworks was 1.2. Having one comorbidity thus increased the risk of having multiple within all subnetworks. Constipation was most strongly related to "*urogenital symptoms and infections*", whereas diarrhoea was most strongly related to "*psychosocial health problems*". The network is shown in figure 15.



Psychosocial health problems	Urogenital symptoms/infections	Somatic symptoms	Musculoskeletal symptoms
1 *Feeling anxious/nervous*	13 *Urination symptoms*	25 *General weakness*	37 *Chest pain NOS*
2 *Acute stress reaction*	14 *Urinary incontinence*	26 *Headache*	38 *Chest symptoms*
3 *Feeling depressed*	15 *Urinary infections*	27 *Migraine*	39 *Muscle pain/symptoms*
4 *Sleep disturbance*	16 *Urinary calculus*	28 *Tension headache*	40 *Hip/leg/foot symptoms*
5 *Anxiety disorder*	17 *Menstruation symptoms*	29 *Hyperventilation syndrome*	41 *Shoulder symptoms*
6 *Somatisation disorder*	18 *Genital symptoms female*	30 *Vertigo / dizziness*	42 *Back symptoms*
7 *Depressive disorder*	19 *Breast symptoms female*	31 *Vertiginous syndrome*	43 *Arm/hand symptoms*
8 *Neurasthenia/surmenage*	20 *Genital candidiasis female*	32 *Heart symptoms*	**Other diagnoses**
9 *Psychological disorder*	21 *Genital infections female*	33 *Involuntary movements*	44 *Concussion*
10 *Fear of disease*	22 *Vaginitis/vulvitis NOS*	34 *Throat symptoms*	45 *Peripheral neuritis*
11 *Relationship problems*	23 *Genital symptoms male*	35 *Respiratory symptoms*	46 *Haemorrhoids*
12 *Health issue other person*	24 *Genital infections male*	36 *Pruritus*	C *Constipation*
			D *Diarrhoea*

Figure 15: Weighted network of 46 health problems associated with IBS. Darker arrows imply larger risk ratios. Colours denote diagnoses with a common ground.

Aim 3. Incidence of health problems in the years around an IBS diagnosis

The health problems from the four subnetworks in aim 2 were, more than other health problems, incident in the ten years before and after the IBS diagnosis (i.e. adjusted incidence rate ratio >1.0, figure 16). For "*psychosocial health problems*" and "*urogenital symptoms and infections*", the adjusted incidence rate ratio was highest in the year of the IBS diagnosis (1.6 and 1.3). For "*musculoskeletal symptoms*" it was high throughout, and as such did not favour incidence before

versus after IBS. The adjusted incidence rate ratio of the subnetwork "*other somatic symptoms*" tended to decrease somewhat after the IBS diagnosis. IBS patients further had an increased incidence of GI infections both before and after the IBS diagnosis, of a magnitude comparable to the increase in urogenital infections. However, there was no increase in GI neoplasms (figure 16).

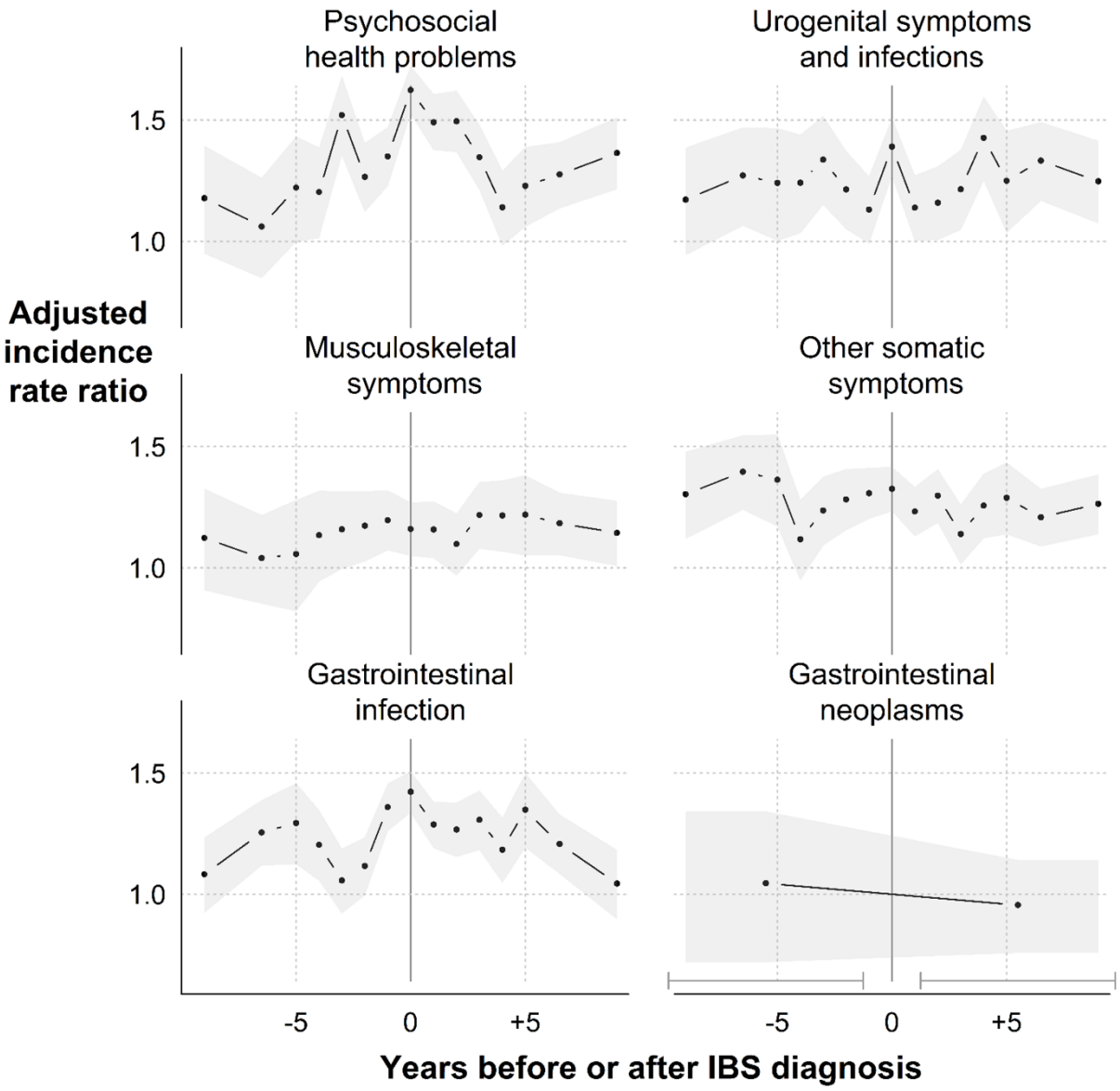


Figure 16: Adjusted incidence rate ratios of four sets of diagnoses. Adjustment is for age, sex, GP practice, and total number of diagnoses; values are the quotient of IBS⁺ / IBS⁻. Shades represent 95% confidence intervals.

Discussion

We show that IBS shares long-term associations with many health problems, specifically (1) *psychosocial health problems*, (2) *urogenital symptoms and infections*, (3) *musculoskeletal symptoms*, and (4) *other somatic symptoms*, which formed four clusters in the "diseasome" of IBS.

Furthermore, we illustrate that psychological and urogenital health problems are often diagnosed in the same year as IBS, rather than structurally preceding or following IBS.

Aim 1. Health problems associated with IBS

The diagnostic categories enriched in the present study are in line with systematic reviews of comorbidities in IBS.[4,7,25-27] Fibromyalgia, a condition involving musculoskeletal pain, is present in around one-third of IBS patients compared to 2% of the general population,[28] which in our study translates to enrichment of musculoskeletal symptoms. Similar to the present study, Whitehead *et al*[7] found many psychiatric diagnoses and urogenital infections to be more common in IBS patients than in matched control groups of non-IBS and patients with inflammatory bowel disease. It remains speculative why urogenital infections are both more prevalent and enriched in IBS patients compared to control groups, including controls with organic GI disease. Whitehead *et al*[7] postulate that such infections may be common in IBS because IBS patients are hypervigilant to somatic symptoms and have a low threshold to consult a physician. Our work supports a theory of an increased pain perception in IBS patients, as most pain-related conditions were amongst diagnostic categories enriched in IBS patients. While it is possible that increased pain perception leads to increased GP consultations, increased investigations, and therefore increased discovery of urogenital infections, it does not explain enrichment of these infections. Moreover, it is likely that the large share of ICPC diagnoses increased in IBS patients compared to patients without a GI disorder is due to biases inherent to matched pairs designs, rather than to GP consultation tendencies. For example, the risk ratio of pregnancy was 1.45, whereas this should neither be driven by a medical relation to IBS nor to consultation tendencies, as consultation for pregnancy is highly common.[24] The factor 1.45 may instead be introduced by comparing a group with at least one confirmed diagnosis to a group without necessarily one diagnosis, and highlights the need for rank-order based interpretations such as using functional enrichment analysis. In summary, enrichment of urogenital infections should not be explained by GP consultation tendencies. Another explanation is misdiagnosis by GPs, which is a limitation of the present study, but should not lead to enrichment of entire diagnostic categories. There may thus be a pathophysiological link between IBS and urogenital infections. Future studies are needed to unravel such a link and its mechanisms (e.g. microbiota,[29,30] immune system,[31] anatomical proximity[32]), which go beyond the scope of the present study.

Comparing IBS patients to controls with organic GI disease yielded similar but weaker results, implying overlap between the comorbidity profiles of IBS and organic GI disease, in which the psychosocial, urogenital, and musculoskeletal, and somatic nature has some specificity to IBS. A similar conclusion was reached by Whitehead *et al*,[7] who found that the prevalence of somatic disorders in inflammatory bowel disease patients was intermediate to that in IBS and non-IBS controls.

Our findings have several implications in addition to the aforesaid. First, all diagnostic subcategories enriched in IBS patients were symptoms, rather than neoplasms or infections (except for urogenital infections), arguing against neoplastic or infectious processes as an explanatory mechanism for IBS, and confirming its symptom-based and benign nature. Second, symptoms enriched in IBS covered multiple organs, which may suggest complex interaction between central and peripheral processes. Third, the comorbidity profile of organic GI disease was intermediate to those of controls without GI diagnosis and IBS patients, which suggests that the majority of comorbidities of IBS are not primarily driven by factors such as inflammation, as this is a hallmark of most organic GI diseases. In summary, we can speculate that central sensitisation or other central mechanisms increasing somatic symptom perception are most compatible with the observed comorbidity pattern of IBS.

Aim 2. Interactions of health problems within the "diseasome" of IBS

The "diseasome" and its four subnetworks are an overview of potentially related co-diagnoses that might share similar aetiologies or could be important to improve the management of IBS. First, if an IBS patient reports pain in the urogenital region, this pain is often associated with genital or urinary tract infections rather than with other somatic symptoms. Pain in urogenital regions should therefore not immediately be assumed to be part of a generalised hypersensitivity to pain driven by central processes, and assessment of urogenital infections may be useful. Second, given the positioning of constipation and diarrhoea in the network, there may be pathophysiological associations of constipation with urogenital infections on the one hand, and diarrhoea and GI infection with anxiety on the other, which is also seen in animal models of GI infection.[33] Third, musculoskeletal and other somatic symptoms were not associated with infection or injury, and were only weakly related to psychosocial health problems, which is in line with the theory of an increased somatic symptom perception as primary driver of somatic comorbidities in IBS. Although the players in the "diseasome" of IBS (i.e. aim 1) have been described in earlier studies,[4-7] we believe this is the first integrative portrayal of the comorbidities of IBS and how they relate to each other.

Aim 3. Incidence of health problems in the years around an IBS diagnosis

By studying the incidence rates of diagnoses in the years around the IBS diagnoses we investigated potential mechanisms underlying comorbidity. As IBS is a disorder of gut-brain interaction, some studies have assessed the directionality of health problems in gut and brain. It has been found that anxiety disorders frequently precede IBS in primary care, and that this directionality supports the theory of anxiety playing a role in the development of IBS in at least some patients.[9,10] While we also find an increased incidence of anxiety disorders before an IBS diagnosis, the adjusted incidence rate ratio for psychosocial health problems was highest in the year of the IBS diagnosis. The same held for urogenital comorbidities, suggesting a direct relation between GI symptoms and urogenital symptoms or infections. Future studies are needed to understand the link between urogenital infections and IBS in the same year, having in mind that these infections were associated with IBS plus constipation rather than diarrhoea or organic GI disease. The increased incidence of GI infections in IBS patients compared to controls has been well-described (i.e. individuals with a GI infection are more likely to develop IBS, and patients with pre-existing GI symptoms are more prone to GI infections,[34] both of which we also find). The increase in GI infections was not higher than that in urogenital infections. Paula *et al*[35] found non-enteric infections to be more predictive of IBS than GI infections. It is possible that (post-infectious) IBS can also be triggered by a non-enteric infection. Finally, Nørgaard *et al*[23] analysed the incidence of colorectal cancer in a design very similar to ours, and found no increased risk between 1 and 10 years after the IBS diagnosis.

One strength of the present study is the large sample, representative of the Flemish general population, with a data period usually exceeding ten years. Besides, although there are many reports on associations between IBS and single comorbidities, we use an integrative approach, i.e. a "diseasome" that shows enrichment of diagnosis categories in IBS, and using a continuous time-axis to assess the directionality of diagnoses. The primary limitation of the present study is reporting bias by GPs. We attempted to address this by matching by GP practice, excluding patients with a short data period, and by using functional enrichment analysis to interpret risk ratios. We also deemed it best to exclude the digestive system ICPC diagnoses as this would introduce biases of various types (e.g. increased GI investigations in IBS patients or confusion diagnoses).[23,36] We included diarrhoea and constipation in the network, but these may not represent stable stool form predominance based subtypes of IBS. A second limitation is that the year of diagnosis may not be the year of symptom onset. Therefore, we also retrieved the incidence over the ten years before and after the IBS diagnosis.

In summary, IBS shares long-term associations with psychosocial health problems, urogenital symptoms and infections, musculoskeletal symptoms, and other somatic symptoms registered in primary care. These associations were stronger in IBS than in organic GI disease, and may thus be driven by factors specific to IBS, such as a generalised hypersensitivity to pain, but most likely not a decreased threshold for GP consultation. Psychosocial and urogenital comorbidities are often diagnosed in the same year as IBS, and do not structurally precede or follow IBS in primary care. Clinicians are encouraged to take comorbidities into account when diagnosing and managing IBS, as this may have important treatment implications.

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Development of Irritable Bowel Syndrome Features Over a 5-year Period

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Abstract

Background & Aims: There are few data from longitudinal studies of the gastrointestinal and psychologic features of irritable bowel syndrome (IBS). We studied within-person correlations among features of IBS, along with progression of gastrointestinal (GI) symptoms and quality of life, and factors associated with changes over time.

Methods: We performed a longitudinal study of 276 patients with IBS in Sweden (70% female; ages, 19–76 years) who completed questionnaires, each year for 5 years, about their GI symptom severity, quality of life, GI-specific anxiety, general anxiety, depression, and coping resources. We performed within-person correlation analyses, latent class growth analysis, and random-intercept cross-lagged panel analysis.

Results: Within-person correlations with GI symptom severity were strongest for quality of life (r=–0.56) and GI-specific anxiety (r=0.47). Progression of GI symptom severity was defined based on 3 classes; the class with the highest mean levels of GI, depression, and (GI-specific) anxiety symptoms at baseline did not improve over the 5-year period, contrary to the other classes. GI-specific anxiety was associated with an increase in GI symptom severity and decrease in quality of life 1 year later (P<.05) but other features of IBS were not.

Conclusions: In a 5-year study of patients with IBS in Sweden, we found 3 classes of GI symptom development. We found levels of GI-specific anxiety to associate with GI symptom severity and quality of life 1 year later. Clinicians should be aware of GI-specific anxiety in patients with IBS, to identify patients at risk for lack of long-term symptom improvement with standard medical treatment.

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder (FGID) defined by chronic and/or recurrent abdominal pain associated with altered bowel habits.[1] However, IBS patients frequently suffer from psychological symptoms as well.[2] IBS prevalence is roughly 10%,[3] and, unfortunately, treatment and clinical management remains suboptimal.[4]

IBS symptoms are thought to wax and wane, without being progressive in the long term. Some studies have followed up IBS patients over several years, showing that the IBS diagnosis is often not continuously present over time,[5] and that symptom severity fluctuates substantially.[6, 7] Others found that improvements in symptom severity after three months predicted improvement after one

year,[8] possibly indicating some consistency in symptom evolution. Improvement was also predicted by anxiety/depression at baseline. This seems counterintuitive, but may be an effect of regression-to-the-mean; patients with severe symptoms at baseline are more likely to improve on average whereas those with mild symptoms are more likely to worsen. Finally, one study reported that in individuals without IBS at baseline, anxiety levels predicted the onset of IBS at a follow-up of twelve years, while in individuals without anxiety at baseline, IBS predicted an increase in anxiety.[9] In summary, the evolution of IBS over time is complex and longitudinal studies are scarce and inconsistent, with a possible but uncertain role for psychological features, in line with the Rome IV conceptualization of FGIDs as disorders of gut-brain interactions.[10]

Further, most of the few published longitudinal IBS studies relied on two data points, whereas more data points are desirable to study symptom evolution. Besides, several psychological features have a cross-sectional association with IBS, such as GI-specific anxiety and coping resources,[11, 12] but their longitudinal relation with IBS symptom severity has not been investigated. Finally, IBS patients are heterogeneous, and results may render more meaningful on the within-person or subgroup level than on the between-person or total sample level. We therefore investigate: 1) longitudinal within-person correlations of IBS features, and 2) evolution of GI symptoms and quality of life, subgroups thereof, and predictors of their changes over time.

Methods

Patients

We used a Swedish longitudinal cohort of 276 adult IBS patients (≥ 18 years old), who were referred to our specialised unit for FGIDs from primary care or through self-referral. During an interview, the medical history was recorded and the diagnosis was made according to Rome II criteria, based on clinical presentation and additional investigations if considered necessary by the gastroenterologist (MS). However, the vast majority of patients who were referred from primary care had already undergone sufficient investigations to rule out other diagnoses with reasonable certainty. All patients were included in different studies assessing the pathophysiology of IBS,[13-17] although not in studies testing a standardised treatment. Exclusion criteria were abnormal results on standard screening laboratory tests, severe psychiatric, systemic, or other GI diseases, allergies, history of drug or alcohol abuse, and the inability to respond to questionnaires in Swedish. All patients gave

written consent to participate after verbal and written information. The study protocol was approved by the Regional Ethical Review Board in Gothenburg prior to enrolment.

Questionnaires

Participants completed questionnaires once annually over five years, covering the following IBS features: GI symptom severity (Gastrointestinal Symptom Rating Scale, GSRS,[18] scale: 1 to 7), which queries the subdomains diarrhoea, constipation, abdominal pain, satiety, indigestion, and reflux; quality of life (IBS-QOL,[19] scale: 0 to 100), which specifically assesses the effect of IBS on quality of life; GI-specific anxiety (Visceral Sensitivity Index, VSI,[20] scale: 0 to 75), which queries fear and anxiety for GI symptoms as endogenous stressor; general anxiety and depression (Hospital Anxiety and Depression scale, HADS,[21] scale: 0 to 21); coping resources (Coping Resources Inventory, CRI,[22] scale: 60 to 240), which queries the way in which people handle stress in its broadest sense.

Other measures

At the start of the study, demographic information was collected, and all patients were subtyped based on the Rome II recommendation.[23] We also recorded if the onset of IBS occurred after a gastroenteritis, i.e. post-infectious IBS (PI-IBS). Participants underwent a barostat protocol, in which a balloon was distended in the rectum with 5 mmHg increments until the first report of pain (details elsewhere[24]). Finally, we quantified oroanal transit time (OATT) in a one-week protocol, where participants ingested ten radiopaque rings every morning, and on the seventh day the rings remaining in the bowel were counted (details elsewhere[16]). This number was divided by the number of rings per day to obtain OATT in days. A normal transit time was defined as 0.7–2.2 days for men and 0.9–4.2 days for women.[25]

Longitudinal within-person correlations of IBS features

We used R version 3.3.3[26] to compute within-person correlations between IBS features. Within-person correlations differ from regular Pearson correlations, which may miss processes relevant to the individual as exemplified in Figure 17. Within-person correlations were computed by, for each participant, centering values on zero prior to computing regular Pearson correlations. Within-person correlations were visualised in a network using the R-package *qgraph*[27].

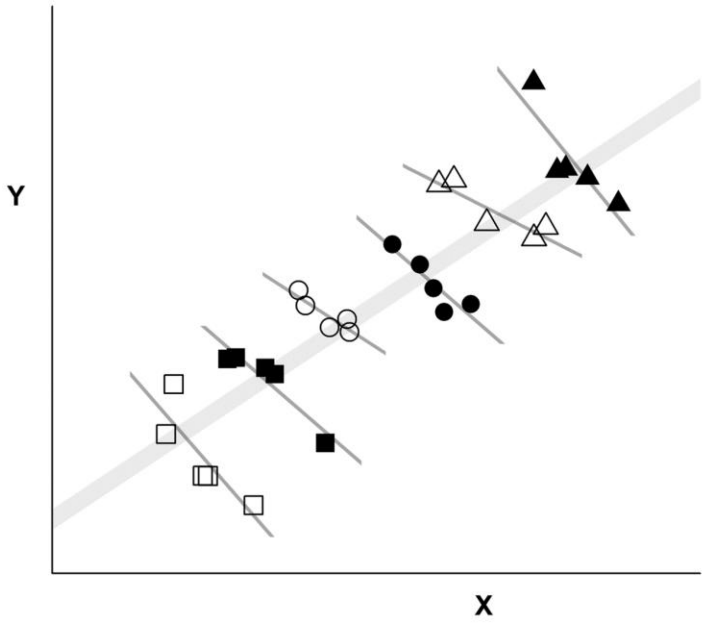

Figure 17: Theoretical example of a relation between X and Y, with six participants and five data points per participant. Here, the regular Pearson correlation (thick line) is very different from the within-person correlation (thin lines). This discrepancy is an example of Simpson's paradox..

Symptom evolution and subgroups thereof

We used Mplus version 7.4[28] to perform two separate latent class growth analyses of GI symptom severity and quality of life. Simply put, this analysis searches for patient subgroups with common symptom evolution trajectories (i.e. "classes"). It does so based on overall severity level ("intercept"), linear development over time ("linear slope"), and u-shaped developments ("quadratic coefficients"). Technically, the number of latent trajectory classes was determined by the minimum Bayesian Information Criterion (BIC), given a statistically significant Lo-Mendell-Rubin adjusted test. Missing data was handled using the full information maximum likelihood (FIML) procedure.

We compared the classes by several baseline characteristics: age, sex, IBS subtype, PI-IBS status, rectal pain threshold, OATT, GI symptom severity, quality of life, GI-specific anxiety, general anxiety, depression, and coping resources. These comparisons were done using analysis of variance, Kruskal-Wallis, or chi-square tests as appropriate.

Prediction of rank order changes in GI symptom severity and quality of life

We used the R-package *lavaan*[29] to create so-called random-intercept cross-lagged panel models of psychological IBS features on the one hand (i.e. GI-specific anxiety, coping resources, general

anxiety, and depression), and IBS outcomes on the other (i.e. GI symptom severity and quality of life). Simply put, these models analyse predictive relations between two variables. For example, it tests whether anxiety at year 0 predicts GI symptom severity at year 1 while controlling for GI symptom severity at year 0. More formally, the technique is from structural equation modelling and investigates lagged associations while controlling for auto-regressive and within-time associations. The technique has been used particularly in social science to assess the directionality of effects (e.g. [30]). Here we selected a cross-lagged model that specifically accounts for heterogeneity.[31] Missing data was handled using the FIML procedure.

Results

IBS cohort

Of the 276 participants, 70% were female, and the age ranged from 19 to 76 years (median 39). All IBS features except coping resources had improving sample averages over the years, and all IBS features had some within-person variation (for example, the median within-person range of all IBS features was greater than one sample standard deviation). Descriptive statistics are in table 6. We compared participants who completed the study to those who dropped out (last available data point was used), and there were no statistically significant differences in any IBS feature (Table 7).

Table 6: Descriptive statistics of selected IBS features in the cohort. Values are means ± SD or counts.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
$N_{NON\text{-}MISSING}$ (≈)	212	194	163	124	105	107
GI symptom severity	3.1 ± 0.8	2.9 ± 0.9	2.9 ± 1.0	2.8 ± 0.9	2.7 ± 0.9	2.7 ± 0.8
Quality of life	66 ± 17	73 ± 16	75 ± 17	77 ± 15	79 ± 15	78 ± 16
GI-specific anxiety	34 ± 17	29 ± 17	25 ± 16	24 ± 16	25 ± 16	25 ± 16
Coping resources	175 ± 22	169 ± 24	171 ± 24	171 ± 25	172 ± 25	172 ± 25
General anxiety	6.9 ± 4.3	6.1 ± 4.0	5.6 ± 4.0	5.5 ± 4.6	5.3 ± 4.0	5.6 ± 3.8
Depression	4.6 ± 3.6	4.1 ± 3.7	3.8 ± 3.6	3.9 ± 3.9	3.6 ± 3.6	3.9 ± 3.4

Table 7: Comparison of drop-outs and non-drop-outs. For drop-outs, the last available value was used.

	Non-drop-out	Drop-out	P-value
GI symptom severity	2.9 ± 0.9	3.0 ± 1.0	0.69
Quality of life	69 ± 20	64 ± 23	0.33
GI-specific anxiety	28 ± 17	29 ± 19	0.70
Coping resources	169 ± 24	174 ± 24	0.32
General anxiety	5.7 ± 4.1	6.4 ± 4.6	0.46
Depression	4.1 ± 3.7	4.1 ± 3.8	0.98

Longitudinal within-person correlations of IBS features

GI symptom severity had strong within-person correlations with quality of life (r=-0.56, p<0.001) and GI-specific anxiety (r=0.47, p<0.001). By contrast, GI symptom severity had weaker within-person correlations with all other psychological variables: depression (r=0.26, p<0.001), general anxiety (r=0.22, p<0.001), and coping resources (r=-0.15, p=0.02). A network is shown in figure 18, with the full correlation matrix in table 8.

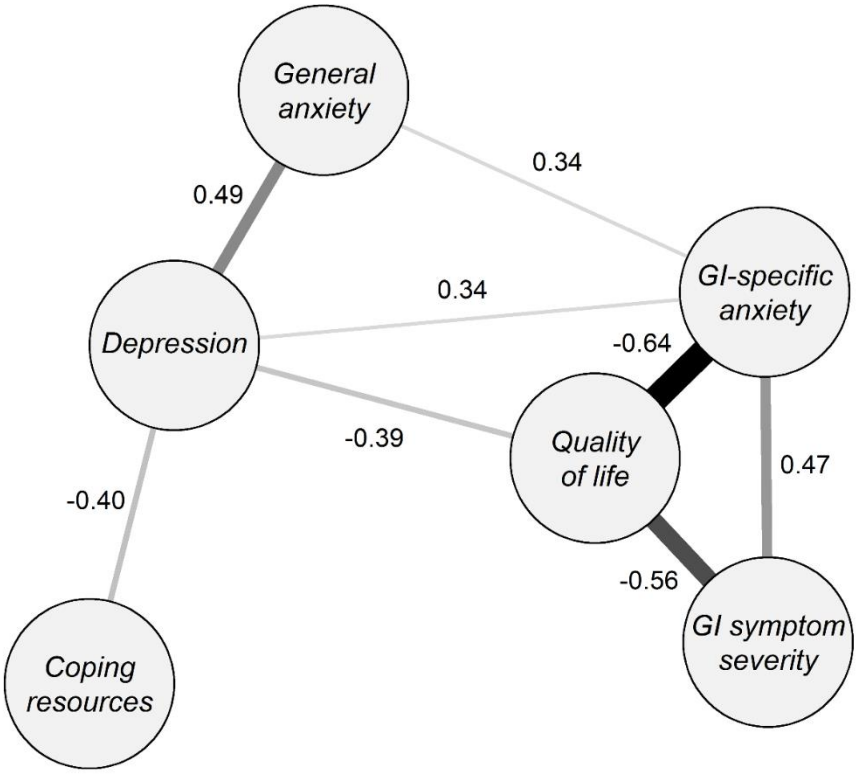

*Figure 18: Network of longitudinal, within-person correlations (r) between six IBS features. Correlations of magnitude |r|<0.3 were made invisible for graphical purposes, but do influence the network. *: p<0.005.*

*Table 8: Correlation matrix of IBS features, with both within-person and between-person correlations. *: p<0.05, **: p<0.001.*

	GI symptom severity	Quality of life	GI-specific anxiety	General anxiety	Depression	Coping resources
GI symptom severity		-0.56**	0.47**	0.22**	0.26**	-0.15*
Quality of life	-0.66**		-0.64**	-0.30**	-0.39**	0.20*
GI-specific anxiety	0.56**	-0.72**		0.34**	0.34**	-0.14*
General anxiety	0.34**	-0.46**	0.43**		0.49**	-0.28**
Depression	0.29**	-0.50**	0.38**	0.64**		-0.40**
Coping resources	-0.18*	0.34**	-0.32**	-0.54**	-0.63**	

Between-person correlations

Within-person correlations

Symptom evolution and subgroups thereof

GI symptom severity evolved by three classes, representing 59, 119, and 36 IBS patients, respectively. The classes differed by overall baseline severity (i.e. intercept, p<0.001), and represent low, intermediate, or high GI symptom severity. To a lesser extent, there was also a difference in slope (p=0.002, i.e. the high GI symptom severity class did on average not improve, whereas the low and intermediate GI symptom severity classes did). The high GI symptom severity class was characterised by the youngest age (p=0.004), largest share of women (p=0.001), smallest share of PI-IBS (p=0.04), lowest rectal pain threshold at baseline (p=0.002), and the worst baseline score on all psychological IBS features except coping resources. Statistics are listed in table 9.

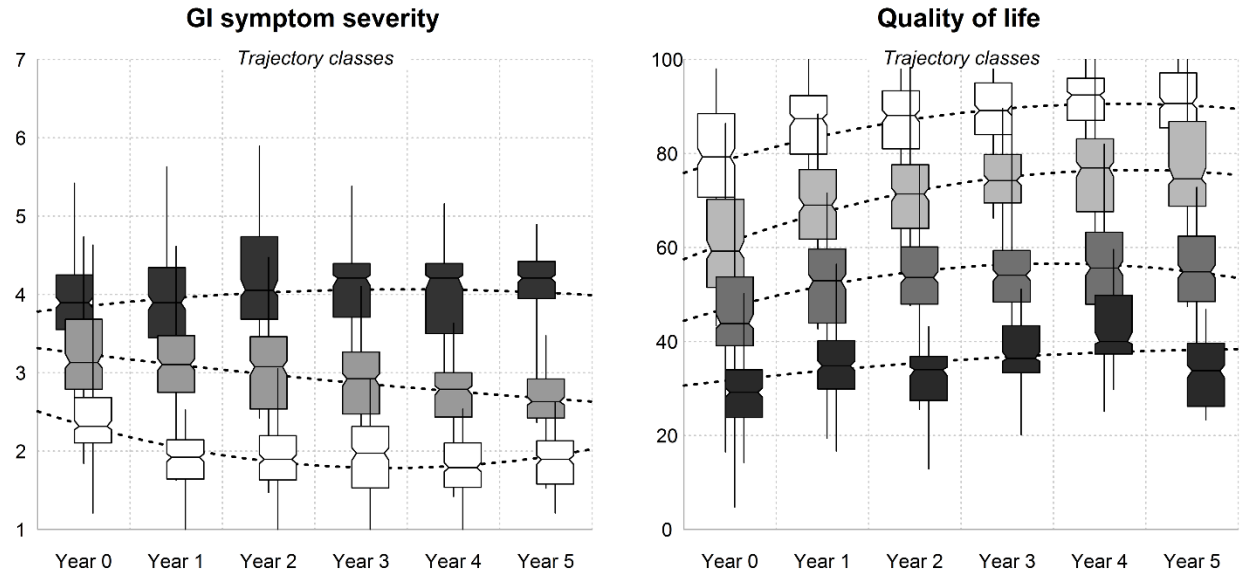

Figure 19: Latent growth classes of GI symptom severity (left) and quality of life (right). Whiskers are minimum and maximum values. GI symptom severity: higher is worse (dark fill); quality of life: higher is better (light fill).

Quality of life evolved by four classes, representing 24, 43, 73, and 67 IBS patients, respectively. The classes differed by overall baseline level (i.e. intercept, p<0.001), and represent low, intermediate (2x), and high quality of life. The classes did not differ in evolution over time. The low quality of life class had the lowest rectal pain threshold at baseline (p=0.002) and the worst baseline scores on all psychological IBS features. Statistics are listed in table 9, and the trajectory classes are visualised in figure 19. The entropies of the two trajectory class solutions were 0.81 and 0.79, respectively.

Table 9: Baseline descriptive statistics of the latent growth classes.

	GI symptom severity				Quality of life				
	Low	Mid	High	P	Low	Mid 1	Mid 2	High	P
N	59	119	36		24	43	73	67	
Intercept	2.3	3.4	3.8	<.001	32	47	61	78	<.001
Slope	-0.3	-0.1	0.1	.002	2	5	7	6	.24
Quadratic coefficient	0.05	0.01	-0.02	.03	-0.18	-0.76	-0.80	-0.66	.70
Age (years)	44 ±13	41 ±14	36 ±11	.004	38 ±12	40 ±15	42 ±15	41 ±12	.41
Female (%)	31 (53)	86 (72)	31 (86)	.001	18 (75)	31 (72)	54 (74)	43 (64)	.52
IBS-C (%)	11 (19)	23 (20)	7 (20)	.19	4 (17)	8 (19)	12 (17)	15 (23)	.78
IBS-D (%)	29 (50)	47 (40)	9 (26)		9 (39)	15 (36)	28 (39)	30 (45)	

IBS-A (%)	18 (31)	47 (40)	19 (54)		10 (43)	19 (45)	32 (44)	21 (32)	
PI-IBS (%)	7 (27)	6 (9)	1 (5)	.04	1 (7)	3 (16)	3 (7)	6 (21)	.28
IBS duration (years)	11 ±7	11 ±8	10 ±5	.78	10 ±5	10 ±5	10 ±7	11 ±7	.63
Rectal pain threshold (mmHg)	41 ±12	36 ±13	31 ±12	.002	30 ±10	32 ±13	36 ±12	40 ±15	.002
Accelerated transit (%)	6 (24)	6 (10)	7 (29)	.17	5 (26)	3 (12)	6 (15)	5 (20)	.56
Delayed transit (%)	3 (12)	14 (23)	5 (21)		6 (32)	4 (16)	8 (20)	4 (16)	
GI symptom severity	2.4 ±0.6	3.2 ±0.6	3.9 ±0.6	<.001	3.7 ±0.6	3.6 ±0.7	3.2 ±0.7	2.7 ±0.7	<.001
Quality of life	74 ±15	58 ±18	41 ±19	<.001	30 ±10	46 ±13	60 ±14	77 ±13	<.001
GI-specific anxiety	23 ±14	34 ±16	44 ±14	<.001	50 ±13	40 ±13	33 ±16	22 ±12	<.001
General anxiety	5 ±4	7 ±4	9 ±5	<.001	10 ±5	8 ±4	7 ±4	4 ±3	<.001
Depression	3 ±4	5 ±3	7 ±4	<.001	9 ±3	5 ±3	4 ±3	3 ±3	<.001
Coping resources	177 ±23	177 ±20	171 ±23	.29	167 ±20	174 ±23	175 ±22	181 ±19	.01

Prediction of changes in GI symptom severity and quality of life

GI-specific anxiety predicted a change in both GI symptom severity (increase, p=0.031) and quality of life (decrease, p=0.050) one year later. Quality of life also predicted a change in GI-specific anxiety one year later (p=0.026). However, coping resources, general anxiety, and depression did not predict a change in either outcome. Random-intercept cross-lagged panel models are shown in figure 20, in which diagonal paths between variables are of particular interest, as they represent predictive relations, whereas horizontal and vertical paths represent stability coefficients, within-time correlations, or correlated change.

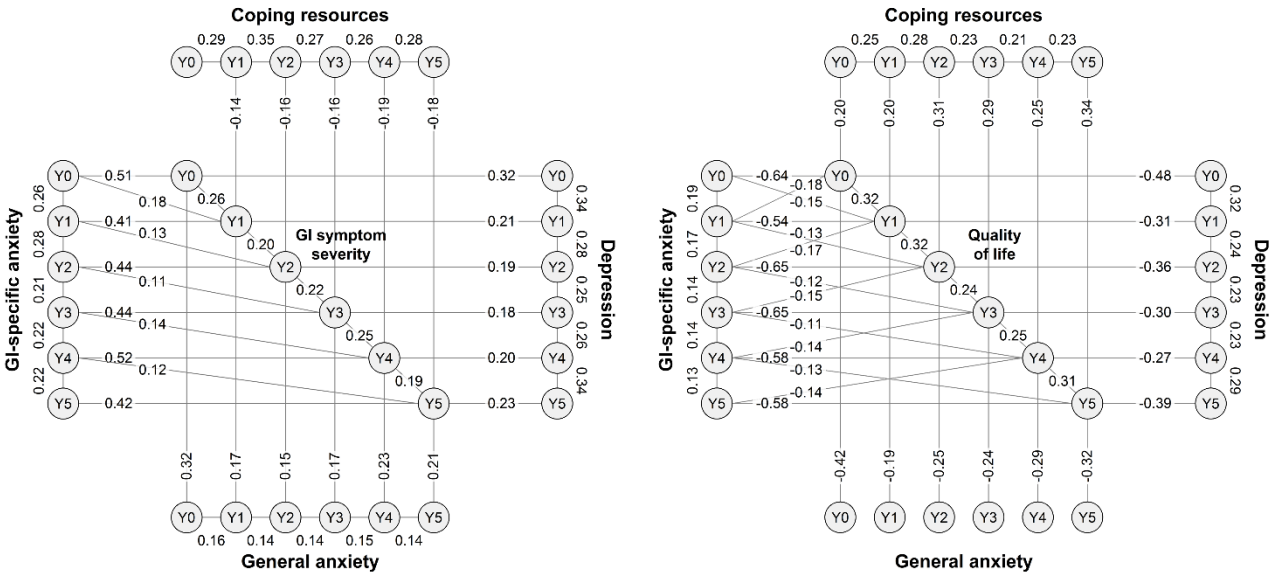

Figure 20: Random-intercept cross-lagged panel models for GI symptom severity and quality of life. Diagonal paths between variables represent predictive relations. Non-statistically significant paths were made invisible for graphical purposes. Values are standardised coefficients.

Discussion

In this study, we show that GI symptom severity has strong within-person correlations with GI-specific anxiety and quality of life, but not with the other psychological IBS features. We further show that GI symptom severity is described by different trajectory classes. The class with the highest GI symptom severity on average did not improve over a five-year period. This class had, compared to the classes of low and intermediate GI symptom severity, the worst baseline scores on various psychological features and the lowest rectal pain threshold, and there was a high proportion of women but a low number of PI-IBS patients. Finally, we show that GI-specific anxiety can predict an increase in GI symptom severity, and decrease in quality of life one year later.

Longitudinal within-person correlations of IBS features

GI symptom severity had strong longitudinal within-person correlations with quality of life and GI-specific anxiety, but only weak correlations with the other psychological IBS features. The key message is thus twofold: first, GI-specific anxiety is positioned as a feature closely related to GI symptom severity. Second, general anxiety, depression, and coping resources are only weakly related to GI symptom severity on the within-person level, so that these psychological features and GI symptom severity are likely to stand in relative isolation. In one within-person analysis,[32] daily

stress was not consistently associated with GI symptoms, which is in line with our conclusions. Labus *et al*,[33] although not using within-person correlations, showed that GI symptom severity was related more strongly to GI-specific anxiety than to other psychological IBS features. Wiklund *et al*[34] found GI symptom severity to be more strongly correlated with quality of life than with general anxiety and depression. Lackner *et al*[11] presented similar results, albeit with different questionnaires. Wilpart *et al*[12] focused on coping resources, and found statistically significant associations between coping and all other tested IBS features. Finally, in the present study, quality of life was in the centre of the network, suggesting that quality of life in IBS is influenced by the totality of IBS features rather than GI symptom severity alone. It has been mentioned before that multiple independent predictors exist of reduced quality of life in IBS, i.e. both intestinal symptoms and psychological factors.[35]

Symptom evolution and subgroups thereof

Three classes of GI symptom severity evolution emerged, and four classes for quality of life. The classes differed chiefly by overall symptom severity ($p<0.001$), but, to a lesser extent, also by linear slope ($p=0.002$). The class of IBS patients with a high mean GI symptom severity had a high mean GI symptom severity in all follow-up years, and did on average not improve. That class was formed by relatively young women, having unselected rather than PI-IBS as well as high psychological symptom scores at baseline. It has been found previously that IBS is somewhat more prevalent with young age[36] and that PI-IBS patients have a slightly better long-term prognosis.[37] Moreover, it has been previously reported that a low rectal pain threshold is cross-sectionally associated with high GI symptom severity,[24] which is in agreement with our results. From our results one may theorise that the more symptomatic IBS patients are more refractory to treatment or sensitive to medication side-effects, and such patients require a specific management strategy. Few studies, however, have specifically portrayed the longitudinal development of IBS features, and those studies usually relied on two data points, so that development trajectories cannot be inferred.

Prediction of rank order changes in GI symptom severity and quality of life

GI-specific anxiety predicted an increase in GI symptom severity and a decrease in quality of life one year later. This brings forward GI-specific anxiety as factor of interest when assessing the severity of GI symptoms and predicting changes over time. No statistically significant predictive relations were found for the other psychological IBS features. Nevertheless, general anxiety and depression

were from the HADS, which queries one's state over the past seven days, and as such may not reflect a general anxiety disorder or trait anxiety. It is still possible that trait anxiety can predict lack of improvement in GI-specific anxiety, GI symptom severity, and quality of life. Few studies investigated predictive relations between IBS features, although depression has been mentioned as negative predictor of treatment effect.[38] Labus *et al*[33] performed path analysis on IBS features, and found GI-specific anxiety to mediate the relation between psychological distress and GI symptom severity, although that analysis was cross-sectional and results are therefore difficult to compare with ours.

Since GI-specific anxiety predicted within-person changes in GI symptom severity and quality of life, it may be considered a key treatment target in IBS patients. Ljótsson *et al*[39] have recently shown in well-controlled clinical trials on internet-based cognitive behaviour therapy (CBT) that exposure and mindfulness components effectively reduce IBS symptoms and GI-specific anxiety, while improving quality of life. More specifically, they demonstrated that the effect on GI symptoms is mediated by a decrease in GI-specific anxiety,[40] supporting the present study in its notion that changes in GI-specific anxiety predict changes in IBS symptom severity. Further, they also confirm that GI-specific anxiety is treatable using CBT, which should therefore be considered a first-line treatment option in IBS patients with GI-specific anxiety. By contrast, IBS patients presenting with general anxiety or depression may require a different approach. More specifically, co-morbid anxiety and depressive disorders should obviously warrant referral to a mental health professional for psychopharmacological and/or or psychotherapeutic treatment, but based on our results, such treatment may have less impact on GI symptom severity or IBS-specific quality of life. The present study and its clinical implications thus highlight the heterogeneity amongst IBS patients and hence the potential need for individually tailored treatment.

One strength of the present study is that we use a longitudinal IBS cohort with six measurement points, allowing to monitor various IBS features over time. Furthermore, we reported within-person, rather than between-person correlations, giving a better understanding of the true relation between the IBS features. The study also has limitations. We had one data point per year, so that we could not quantify fluctuations within the year. Besides, latent class growth analyses are highly sensitive, introducing a risk for chance-based classifications.[41] It also cannot be stated that individual patients belong to a specific class, as class assignment is based on probability. To investigate symptom patterns of individual IBS patients and short-term fluctuations, different symptom

monitoring approaches are needed, such as symptom diaries with a higher sampling frequency, although these will inherently be limited to shorter follow-up periods. Having information about treatment or medication side-effects would also have been desirable, in order to understand better why one class of patients does not improve over time. Furthermore, it is possible that patients are more likely to accept to be part of a study when they are in a symptomatic phase, thereby influencing the pattern of symptom evolution. Finally, the drop-out rate was rather high, although participants who completed or dropped out of the study did not differ on any baseline IBS feature.

In summary, we show that GI symptom severity can be described by different classes of evolution, and that these classes are associated with multiple baseline IBS-related features, such as psychological comorbidity, rectal sensitivity, post-infectious origin of IBS, age, and sex. GI symptom severity is strongly related to GI-specific anxiety, but not to general anxiety, depression, or coping resources, which are likely to stand in relative isolation from GI symptom severity. Finally, GI-specific anxiety can predict a change in GI symptom severity and quality of life one year later. Clinicians are recommended to be particularly attentive to GI-specific anxiety in IBS patients and refer patients for treatment targeting this key IBS feature, such as CBT.

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Relations between food intake, psychological distress, and gastrointestinal symptoms: a diary study

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Abstract

Background: Gastrointestinal (GI) symptoms can be triggered by food intake and psychological distress, but individual-level research on food-symptom and stress-symptom associations is scarce.

Objective: We aimed to identify associations between food intake, psychological distress, and GI symptoms, and their implications for personalised clinical management.

Methods: Through the mobile phone application "*mySymptoms*", 163 users kept, for a median of 5 weeks, a diary of food intake, psychological distress, and GI symptoms. We quantified associations between these on the individual level. The presence of individual-level associations was compared over latent classes of daily symptom patterns.

Results: Various GI symptoms had demonstrable food-symptom associations (heartburn: 73%, discomfort: 67%, diarrhoea: 57%, bloating: 53%, and gas: 48%). Food-symptom associations for pain in the abdomen (33%) were concentrated in the latent class of individuals with pain in the morning (68%), rather than those with pain in the evening and night (27% and 10%, respectively, $p < 0.001$). Stress-symptom relations were also found, although only 18% of individuals reported psychological distress.

Conclusion: Personal food-symptom and stress-symptom relations can be detected, and may translate into specific daily symptom patterns. A next step will be to let personal food-symptom and stress-symptom relations serve as basis for personalised clinical management.

Introduction

Most of us are familiar with them: gastrointestinal (GI) symptoms such as abdominal pain, discomfort, bloating, gas, diarrhoea, nausea, and belching. GI symptoms are bothersome, often recurrent, and can impair quality of life[1]. The prevalence of GI symptoms is high, with a population-based study suggesting 62% for at least one GI symptom[2], and 35% for at least one functional GI disorder (FGID)[3] according to the Rome IV criteria[4]. The pathophysiology of FGIDs is complex and heterogeneous, so that existing pharmacological, psychological, and dietary management strategies often have limited success[5].

One way to study the heterogeneous pathophysiology of GI symptoms is through symptom patterns. If the human body is a black box, symptom patterns are its direct output, and can thus teach us about processes inside. A good example is food intake: symptom patterns often correspond to the intake of specific food products[6-7]. Food-symptom associations can be objectively identified

within an individual. The details of the association (which food group, what delay to symptom onset) give person-specific insights into the mechanism, and thus provide a tool for symptom improvement. Another example is time of the day: an individual's GI symptoms often follow a consistent circadian pattern[8], which may reflect processes directly or indirectly regulated by the circadian clock[9-10]. Studying symptom patterns also addresses patient heterogeneity by identifying relevant patient subgroups, which may help to personalise clinical management of GI symptoms.

Currently, however, symptom patterns are not used at their full potential in symptom management. Although the current Rome IV classification of functional GI disorders is symptom-based and distinguishes around 30 functional GI disorders[4], it has been noted that these show overlap and fluidity over time, and that treatment responses are heterogeneous[11]. Moreover, fine-grained factors such as the diet and psychological distress are missing despite their demonstrated importance[6,12], as are longitudinal features of symptom patterns such as fluctuations with time of the day[13]. In conclusion, there is a need for more detailed studies that use GI symptom patterns as basis for personalised management strategies, and that identify patient subgroups that predict treatment response.

We therefore studied longitudinal patterns of various GI symptoms by using food/symptom diaries. Specifically, we analysed temporal relations between GI symptoms, as well as food-symptom and stress-symptom relations. We further tested whether the presence of a food-symptom or stress-symptom association could be predicted by the symptom pattern during the day.

Methods

This study used anonymous diaries of food intake, psychological distress, and GI symptoms, as kept on the mobile phone application "*mySymptoms*" (SkyGazer Labs ltd, courtesy of CEO Darren Launders)[14]. Users of *mySymptoms* were invited from within the application to opt-in and retrospectively share their anonymous diaries for the present study. With the invitation came a study description, which told about the purpose of the study and data handling. Since data was anonymous (i.e. not encoded), the ethics committee of KU Leuven saw no need for ethics assessment.

Keeping a diary on *mySymptoms* works as follows. Users enter their food intake and symptoms whenever they deem this necessary (i.e. without instructions). Foods and its quantities are reported as free text input, although suggestions are given by autocomplete whilst typing. Reporting food

quantities is optional. Symptoms and psychological distress can be selected from a list, although free text input is also possible. Symptom severity is always on a scale from 1 to 10. Time stamps default to the current time, rounded by the minute, but can also be user-specified.

Diary data pre-processing

Data was handled per diary using R version 3.5.1[15]. First, food quantities were homogenised. For each unique item, we standardised the median quantities of weight units, volume units, and other units to 1, with the maximum capped at 10 to reduce the influence of incorrect values. Second, data was restructured from free text to predefined categories, using a multilingual in-house developed text recognition library. It recognised strings in full (e.g. "[macaroni]"), parts of strings (e.g. "[macaroni] with [tomato sauce] and [cheese]"), and multi-category foods (e.g. "[Caesar salad]"). Strings of at least 7 characters were allowed misspellings at a Damerau-Levenshtein distance[16] of 1 in the R-package *stringdist*[17]. Third, to ensure both analytic feasibility and interpretability, we pooled categories from specific (e.g. sunflower seeds, 86 food categories) to intermediate (e.g. seeds, 28 food categories) or broad (e.g. nuts and seeds, 14 food categories), until there were at least 5 occurrences of that category. The same procedure applied to symptoms. We added two further variables. Consumption frequency was the running sum of caloric food consumption occurrences in the past 24 hours. Night-time consumption was computed from caloric food intake, where intakes between 01:00-04:00 were scored a 2, those between 22:00-01:00 were scored a 1, and others a 0. Geographic origin was estimated using the R-package *gtrendsR*[18], where all free text strings were scored by country-level Google search frequencies, and the country with the largest score was taken. Finally, as quality control, days with fewer than 2 food reports were interpreted as missing data, and we excluded diaries with fewer than 5 symptom occurrences as any further analyses would lack reliability (this was the case for 11 out of the original 174 diaries).

Temporal relations between GI symptoms

We computed within-person correlations between all reported symptoms. Briefly, symptom severity was summed for each day's morning (04:00-12:00), afternoon (12:00-18:00), and evening/night (18:00-04:00). The resolution of three values per day was arbitrarily chosen to best capture lagged associations. Correlations were computed and pooled meta-analytically using the R-

package *metacor*[19] (DerSimonian-Laird approach) and visualised in a network using the R-packages *qgraph*[20] and *plotrix*[21].

Symptom patterns during the day

We did a latent class analysis on symptom patterns during the day. Briefly, per symptom per diary, symptom severity was summed by the hour. A personal min-max normalised mean curve was created (i.e. one curve per symptom per person). Subsequently, for each between-person dyad of curves for a given symptom, we obtained a similarity metric through an optimisation algorithm: we maximised the correlation between the curves by giving every hourly value a one-time opportunity to (partially) shift up to 2 hours ahead or backwards. The individual with the most correlations larger than 0.5 was identified, and all individuals correlating with this person at $r > 0.5$ formed a latent class. This process was repeated until exhaustion of the list of unclassified individuals.

Food-symptom and stress-symptom relations

We investigated associations between food variables and symptoms, as well as psychological distress and symptoms. For every intake of every food category of every diary, we multiplied the quantity by the symptom severity in the next 8 hours minus the previous 8 hours (the latter prevents three biases: reverse causation, changes in reporting style, and long-term developments such as lifestyle changes and regression-to-the-mean), and the sum was taken. This process was repeated at 10.000 iterations, where intake instances were randomly repositioned between days, but not within days, thereby adjusting for circadian patterns and sleep times. From the resulting null-distribution we computed p-values (also for psychological distress). The geometric mean of the top-3 food products was recomputed at 1.000 iterations, where, this time, symptoms were randomly repositioned between days, and a single food-symptom association p-value was obtained. Subsequently, the population-level number of p-values above 0.5 was subtracted from that below 0.5 and expressed as a percentage with 95% confidence using the Pearson-Klopper method of the R-package *binom*[22]. The resulting percentages at the group level were compared across the latent classes of symptom patterns during the day using Fisher's exact test.

Finally, we explored other diet habits over the latent classes of symptom patterns during the day. This was done for the median time of latest caloric food consumption of the day (midnight until 4 AM was considered part of the previous day), the percentage of all caloric food consumptions that

were alcoholic beverages, the principal dietary components, the usage of probiotics, and the avoidance of gluten or lactose as extracted from free-text strings (e.g. containing "gluten-free" or "without gluten"). Statistical comparisons were done with Kruskal-Wallis tests.

Results

We received 163 diaries. Most were fully in English (138, 85%), and originated from North America, Europe, or Oceania (158, 97%). The median diary length was 36 days (interquartile range 24-84 days). Reported symptoms (with number of individuals in parentheses) were: pain in abdomen (n=110), gas (n=91), bloating (n=86), nausea / vomiting (n=51), fatigue (n=41), psychological distress (n=30), headache (n=30), heartburn (n=30), diarrhoea (n=27), discomfort (n=18), belching (n=15), and various somatic symptoms (n=102).

Temporal relations between GI symptoms

Within-person correlations were strongest between pain in the abdomen, bloating, and gas ($r \geq 0.36$, figure 21). Discomfort in the abdomen was related to this triad, as well as to belching, nausea/vomiting, heartburn, and, uniquely, to psychological distress ($r = 0.41$). All discussed correlations and most others differed from 0 with statistical significance at $p < 0.001$ (for a full correlation matrix, see table 10).

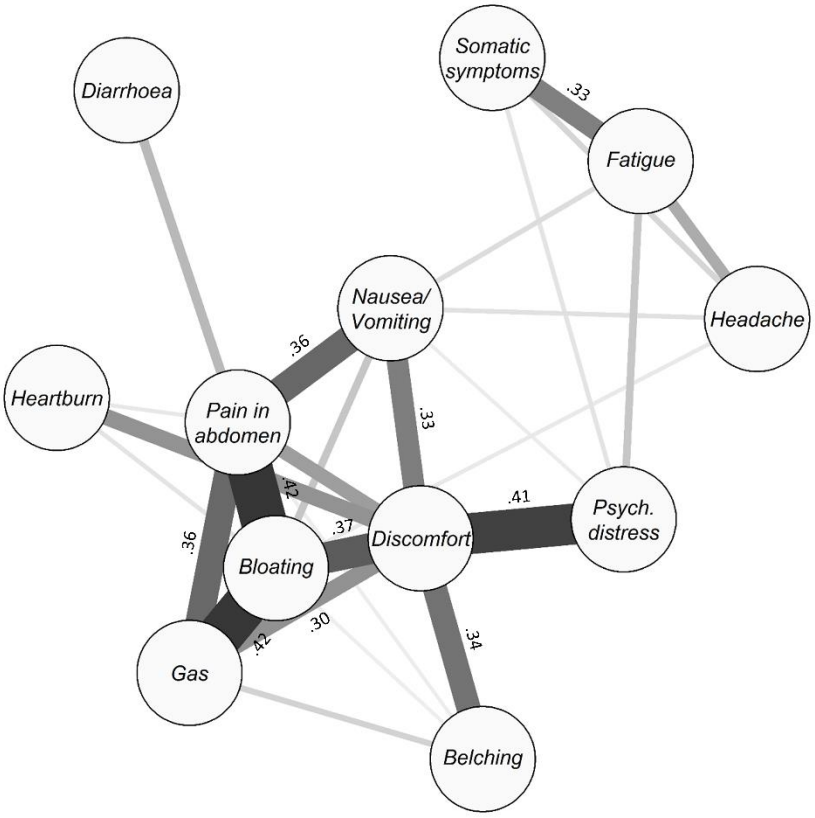

Figure 21: Network of within-person correlations between symptoms. Thickness and colour of lines are proportional to the correlation values, which are displayed in case r > 0.30.

*Table 10: Within-person correlations (r) between symptoms. ***: p < 0.001, **: p < 0.01, *: p < 0.05.*

	Pain in abdomen	Bloating	Nausea / Vomiting	Somatic symptoms	Headache	Gas	Discomfort	Heartburn	Fatigue	Diarrhoea	Psychological distress	Belching
Pain in abdomen		***	***	***	***	***	***	***	***	***	***	***
Bloating	0.42		***	***	***	***	***	***	***	**	***	***
Nausea / Vomiting	0.36	0.23		***	***	***	**	**	***	***	***	**
Somatic symptoms	0.16	0.14	0.17		***	***	***	***	***	**	***	***
Headache	0.16	0.19	0.20	0.21		***		*	***		*	
Gas	0.36	0.42	0.17	0.11	0.10		***	***	**	***	**	***
Discomfort	0.29	0.37	0.33	0.16	0.05	0.30		**	***	**	***	***
Heartburn	0.19	0.20	0.16	0.14	0.10	0.12	0.30		**	*	**	***
Fatigue	0.14	0.16	0.20	0.33	0.27	0.08	0.15	0.13		*	***	**
Diarrhoea	0.25	0.12	0.15	0.09	0.09	0.09	0.14	0.10	0.06			*
Psych. distress	0.15	0.13	0.18	0.20	0.12	0.11	0.41	0.10	0.23	0.05		**
Belching	0.18	0.18	0.16	0.14	0.03	0.22	0.34	0.12	0.13	0.14	0.11	

Symptom patterns during the day

Pain in the abdomen, bloating, and gas had a highly similar average symptom pattern during the day. These symptoms were generally mild in the morning (e.g. up to 11 AM), then worsening until night-time, with particular presence in the evening (figure 22).

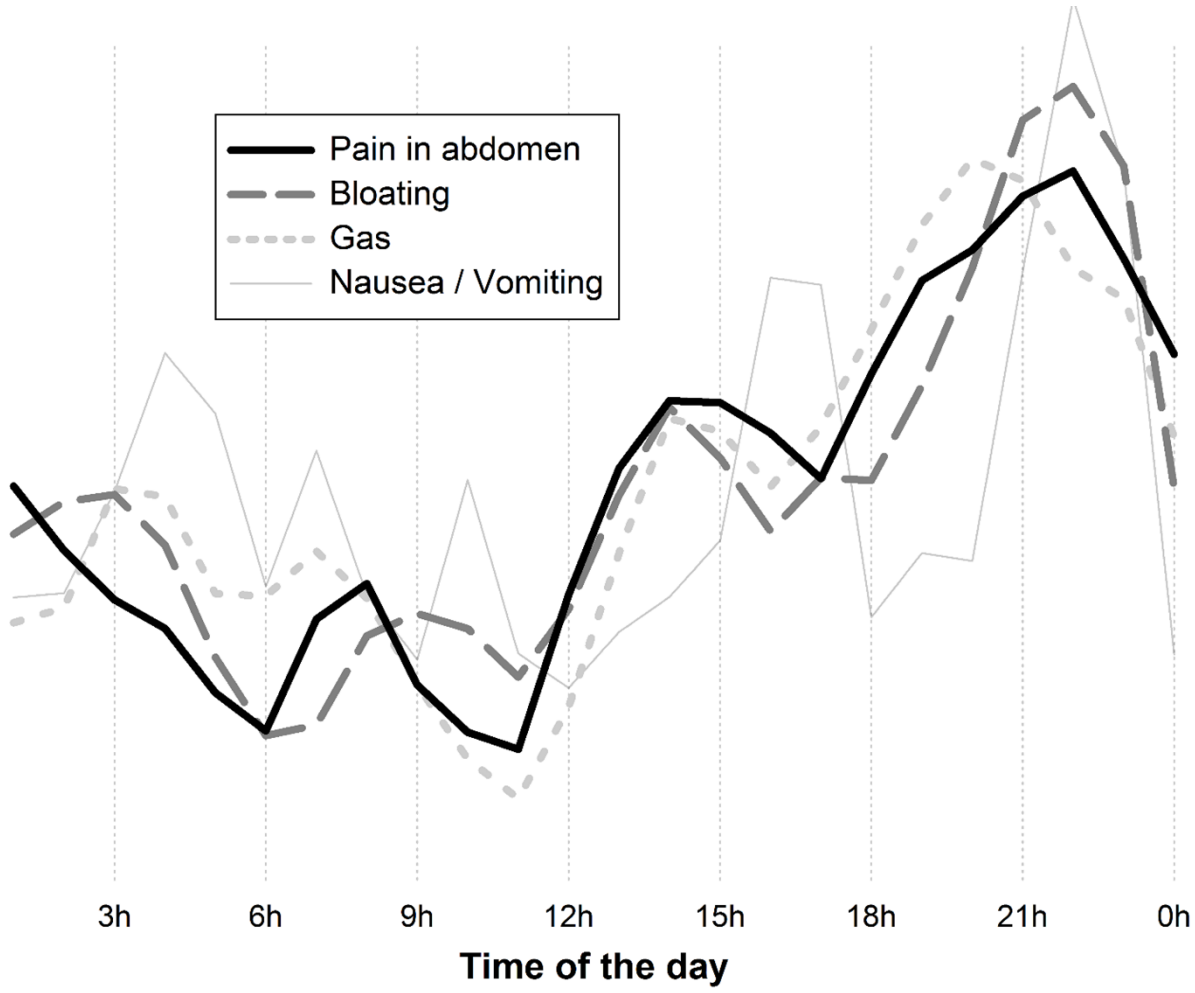

Figure 22: Symptom pattern during the day: curve of the averages.

However, there was inter-individual variability in the symptom pattern during the day (figure 23). Roughly half of individuals with pain in the abdomen, bloating, and gas followed the average pattern, i.e. increasing throughout the day. Another one-fourth to one-third of individuals had night-time symptoms, typically present around 3 to 4 AM. Finally, there was a class of individuals with symptoms in the morning, around 9 to 10 AM. The classification for nausea/vomiting was different, with symptoms occurring in the evening/night (~40%), afternoon (~40%), or night/morning (~20%). Latent class analyses for other symptoms were not performed as there were too few individuals.

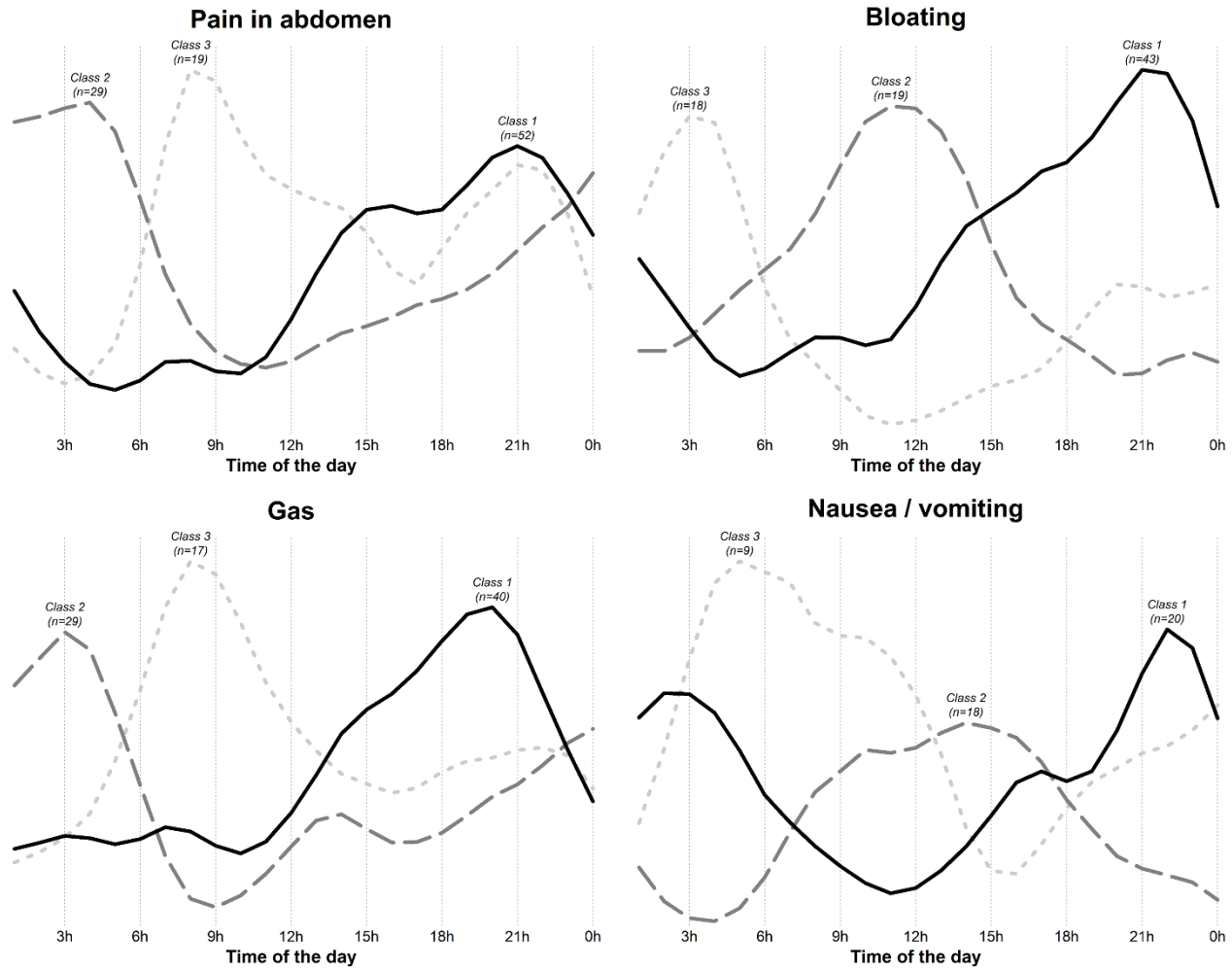

Figure 23: Latent classes of symptom pattern during the day: curves of class averages.

Food-symptom and stress-symptom relations

Associations between food variables and symptoms were demonstrably present in many individuals (figure 24A), in particular for heartburn (73%), discomfort (67%), diarrhoea (57%), bloating (53%), and gas (48%). Food-symptom associations were less prevalent for pain in the abdomen (33%), but were concentrated in the latent class of individuals with pain in the morning, i.e. class 3 (68%), rather than the classes of individuals with pain in the evening and night (27% and 10%, respectively, $p < 0.001$). Extra-intestinal symptoms such as headache and fatigue were not demonstrably triggered by food.

Associations between psychological distress and symptoms were demonstrably present for all symptoms, although only 18% of individuals actually reported psychological distress. Stress-symptom relations emerged especially for symptoms where food-symptom relations were absent (headache: 85%, fatigue: 56%, nausea/vomiting: 65%, figure 24B).

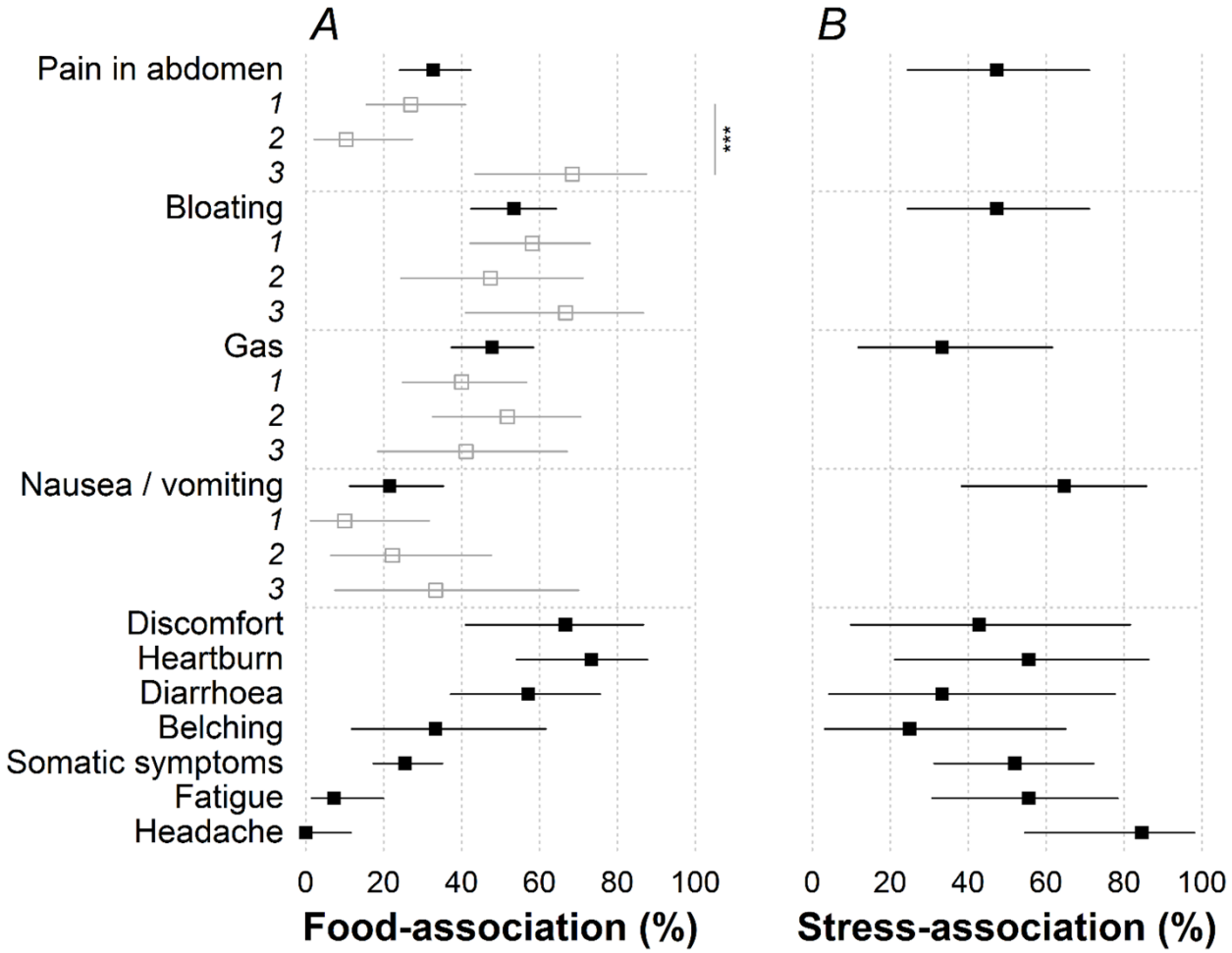

*Figure 24: Percentage of individuals with a demonstrable association between food intake and symptoms (A) and between psychological distress and symptoms (B). Also shown for the latent classes of symptom patterns during the day (grey) wherever statistical power allows it. Whiskers are 95% confidence intervals. ***: $p < 0.001$, **: $p < 0.01$, *: $p < 0.05$.*

In this study population, the average individual still had a caloric food consumption after midnight on most days. Late caloric food consumptions were common amongst individuals with night-time symptoms, such as pain in the abdomen, bloating, gas, and nausea/vomiting (classes 2, 3, 2, and 3, respectively), more so than individuals with daytime symptoms ($p < 0.05$, figure 25A). The night-time symptom classes were further characterised by a higher intake of alcoholic beverages (which constituted > 1% of all reported caloric food consumptions, figure 25B). We further observed trends of gluten-exclusion in individuals with pain in the abdomen, usage of probiotics in diarrhoea, and health-conscious diet profiles in belching (not shown). Symptoms did not differ between weekdays and weekend days.

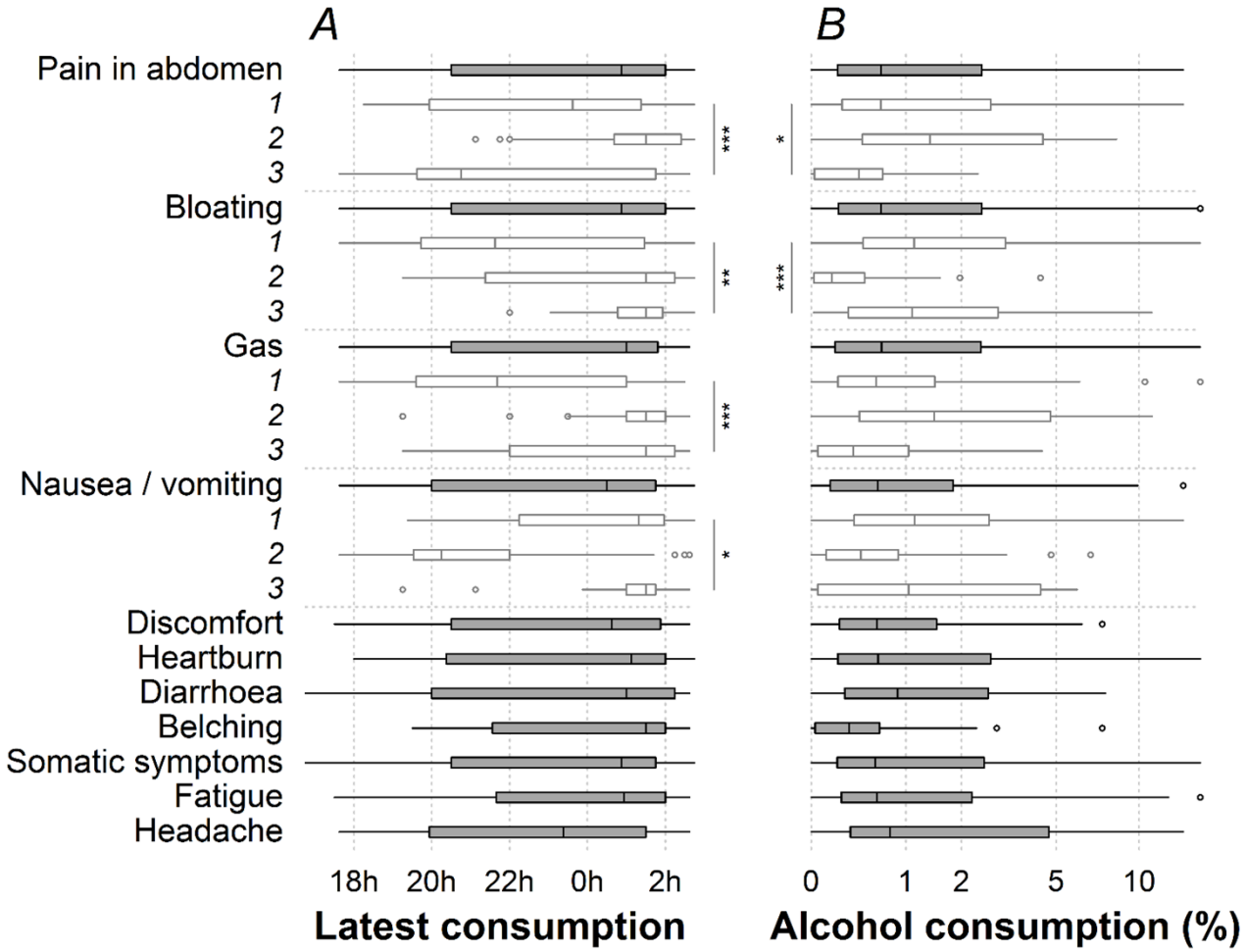

*Figure 25: Median time of the latest caloric food consumption (A) and the percentage of all caloric consumptions that were alcoholic beverages (B, log-2 scale). Also shown for the latent classes of symptom patterns during the day (open boxes). ***: p < 0.001, **: p < 0.01, *: p < 0.05.*

Discussion

This study analysed GI symptom patterns and their relation to time of the day, food intake and psychological distress, generating potential implications for personalised clinical management. We empirically show the existence of personal food-symptom, stress-symptom, and symptom-symptom relations for various GI symptoms. We further show that the presence of food-symptom relations may be associated with latent classes of specific daily symptom patterns (e.g. morning-predominant abdominal pain).

Symptom-symptom relations were strong, especially for pain in the abdomen, bloating, gas, and discomfort. While the comorbidity of these GI symptoms is well-described[23], we show here that these symptoms also tend to co-occur during the same part of the day. It is tempting to speculate about causal paths where gas causes abdominal distension or bloating[24], and that this presents as

painful sensation, although in some individuals pain could also be cramps associated with diarrhoea. Discomfort was the most central node in the network of within-person correlations, and was uniquely correlated with psychological distress, suggesting clinical relevance. However, the definition and significance of discomfort have been debated[25], as a result of which discomfort has been removed from the Rome criteria for irritable bowel syndrome[4,26]. Since discomfort was not in the list of selectable symptoms on *mySymptoms*, we relied on free text input to define discomfort, and included strings such as "gut discomfort", "unpleasant feeling", "nervous tummy", and "upset stomach". One could comment that, on the one hand, 11% of users apparently felt a sensation not covered by any of the selectable symptoms, and took the trouble to explicitly add this symptom, suggesting that abdominal discomfort should be seen as separate entity. On the other hand, discomfort was strongly related to six GI symptoms, so that its meaning and underlying processes may differ between individuals.

There were three latent classes of daily symptom pattern for pain in the abdomen, bloating, and gas. Evening symptoms formed the largest class (e.g. bloating: 54% of the studied population), which is in line with earlier studies[8,27], where 73% of irritable bowel syndrome patients self-reported a similar pattern for bloating. We found two more latent classes, however, for night-time and morning symptoms, respectively. The latent classes of daily symptom pattern may reflect different pathophysiological processes, FGIDs, or even different symptoms[13], and, if so, could be used to guide personalised management. Indeed, the class of individuals with abdominal pain in the morning was characterised by demonstrable food-symptom relations, suggesting that dietary interventions to reduce abdominal pain have more potential in this class than in the classes of evening and night-time pain. Individuals with night-time pain often consumed food deep into the night, and normalising diet habits may be of help. It is conceivable that stress-symptom relations, too, differ across the latent classes, although the present study lacked power to test this, as only 18% of individuals reported psychological distress. The true prevalence of stress-symptom relations is therefore probably lower, as also suggested in one study, where 34% of irritable bowel syndrome patients self-reported that bloating was worse with psychological distress whereas 82% perceived a link with eating[27]. An interesting notion is that symptoms with demonstrable food-symptom relations tended to have fewer stress-symptom relations and vice versa, so that psychological therapies may be successful in case dietary interventions fail. Replication of our results in more extensively phenotyped (FGID) patient populations is warranted.

It will be exciting to take food-symptom and stress-symptom relations fully to the individual level, and let this be a data-driven basis for personalised clinical management. Specifically, diary platforms such as *mySymptoms* could aid in identifying potential food intolerances, for which diaries of ~4 weeks apparently suffice, followed by controlled exclusion of the trigger foods. Another opportunity is to couple the symptom patterns found using a diary to results of an actual pharmacological, psychological, or dietary intervention, and/or to biomarkers in the same individuals. A comprehensive study would account for potentially relevant factors such as psychological distress, the use of medications, and sleep. Standardised protocols and thorough phenotyping of participants are therefore important. The present study provides the basis for and takes a first step towards exploiting these opportunities.

Limitations of the present study include that the study population was anonymous, and no diagnoses, age, or sex are known. Irritable bowel syndrome will be common given that most reported recurrent abdominal pain, and, given the functionality of *mySymptoms*, it is likely that food-symptom associations are more common than in most FGID populations. It is also possible that the prevalence of food-symptom and stress-symptom relations differs between cultures and countries, because of differences in factors such as eating habits, gut microbiota, genetics, availability of treatments, and diagnostics of GI disorders. For example, in populations with an increased incidence of GI infections, infections can explain a share of the symptomatology, and thus fewer demonstrable food-symptom relations are expected. Large-scale international studies could shed light on this issue. We further could not account for medicine usage, sleep, the female menstrual cycle[28], and the presence of GI infection or inflammation. Moreover, *mySymptoms* uses the term "gas" rather than "flatulence", and consequently some users may not differentiate between flatulence, belching, and abdominal distension (bloating was a separate choice option). Finally, there are residual biases such as misreporting and selection bias.

In conclusion, personal food-symptom and stress-symptom relations, as well as associations amongst different GI symptoms can be detected, and may translate into specific daily symptom patterns. A next step will be to let personal food-symptom and stress-symptom relations serve as basis for personalised clinical management.

Acknowledgements

The authors would like to thank Mr Darren Launders, CEO of SkyGazer Labs, for offering the application *mySymptoms* and inviting its users to share their data for the present study.

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Food-symptom diaries can generate personalised lifestyle advice for managing gastrointestinal symptoms

Personalised nutrition for GI symptoms

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Abstract

Background: Gastrointestinal (GI) symptoms have a heterogeneous pathophysiology. Yet, clinical management uses group-level strategies. There is a need for studies exploring personalised management options in patients with GI symptoms.

Objective: From diaries of GI symptoms, food intake, and psychological distress, we extracted and validated personalised lifestyle advice. Second, we investigated group-level GI symptom triggers using meta-analysis.

Methods: We collected 209 diaries of GI symptoms, food intake, and psychological distress, coming from 3 cohorts of patients with GI symptoms (n = 20, 26, and 163, median lengths 24, 17, and 38 days). Diaries were split into training and test data, analysed, and the triggers emerging from the training data were tested in the test data. In addition, we did a random effects meta-analysis on the full data to establish the most common GI symptom triggers.

Results: Analysis of the training data allowed us to predict symptom triggers in the test data ($r=0.27$, $p<0.001$), especially in the subset of patients with a strong global association between lifestyle factors and symptoms ($r=0.45$, $p<0.001$). Low exposure to these triggers in the test data was associated with symptom reduction ($p=0.043$). Meta-analysis showed that caloric intake in the late evening or night predicted an increase in GI symptoms, especially bloating. Several food-symptom associations were found, whereas psychological distress did not clearly lead to more severe GI symptoms.

Conclusion: Diaries of GI symptoms, food intake, and psychological distress can lead to meaningful personalised lifestyle advice in subsets of patients.

Introduction

Gastrointestinal (GI) symptoms such as abdominal pain, bloating, flatulence, and diarrhoea are common in irritable bowel syndrome (IBS) and other functional GI disorders. In these disorders, GI symptoms are influenced, in part, by lifestyle factors such as food intake[1], psychological distress[2], quality of sleep[3], and exercise[4]. Therefore, the clinical management of disorders such as IBS often involves lifestyle advice including dietary interventions (e.g. guidelines of the National Institute of Health and Care Excellence, NICE[5], diet low in fermentable oligo-, di-, and monosaccharides and polyols, FODMAPs[6]) and/or psychological interventions (e.g. cognitive behavioural therapy[7] and hypnotherapy[8]). Results of these strategies are favourable, with typically around half of patients

experiencing adequate symptom relief[9], although parts of this benefit may be attributable to the placebo effect[10].

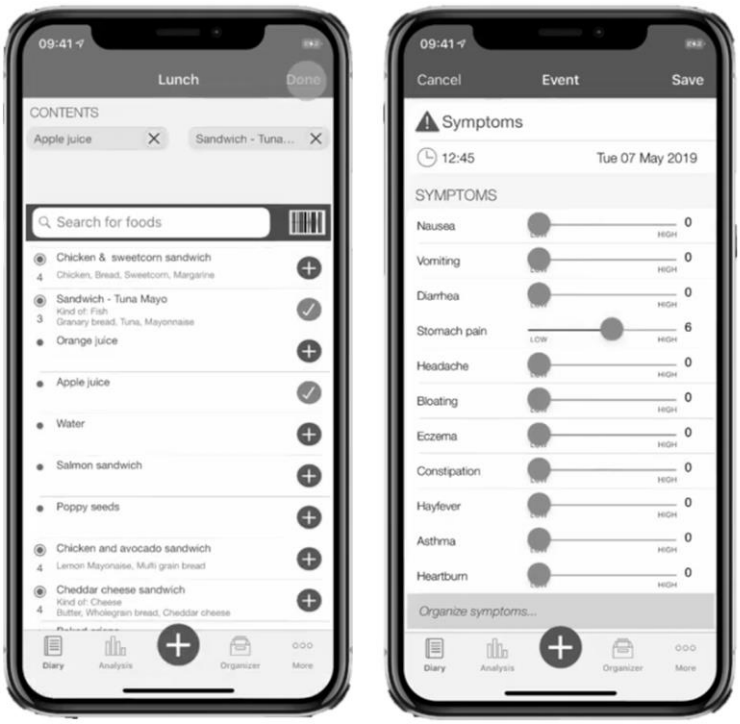
However, treatment responses are heterogeneous, as are the mechanisms underlying symptom onset. For example, dietary intolerances are highly variable and reflect many underlying mechanisms (e.g. effects of stimulants on GI motility, changes in osmolarity or volume, or activation of local immune cells by food antigens, leading to visceral hypersensitivity)[11]. For some patients, psychological distress or a non-lifestyle factor will be more important than the diet. Finally, some relevant mechanisms will be unknown, and are thus currently overlooked when managing GI symptoms based on *a priori* hypotheses. There is thus a need to go from group-level to person-level management of GI symptoms.

Personalised management of GI symptoms in IBS can be achieved, amongst others, when a patient keeps a diary of their symptoms as well as lifestyle factors such as food intake, psychological distress, and exercise. Many dietitians routinely request clients with GI symptoms to keep such a diary, although these diaries are then typically assessed 'with the bare eye', raising questions about the accuracy of the advice – besides the accuracy of the diary. Furthermore, diary analysis is rather laborious, especially if one wishes to account for all of various biases, and therefore it requires computer automation. Several apps exist where one can keep a diary of symptoms and lifestyle factors, but the quality of their advice has not been published. We have developed an automated algorithm[1] to analyse diaries (n=163) kept on the smartphone application *mySymptoms*[12], and found demonstrable food-symptom relations in half to two-thirds of participants depending on the symptom. However, the participants were anonymous, and it was thus unclear whether these had a functional GI disorder. Furthermore, the trigger identification algorithm was not validated in that study.

Therefore, the present study had two aims. First, we aimed to test internal validity of the trigger identification algorithm. Second, we aimed to report the most common symptom triggers in a better characterised study population.

Methods

The present study used three cohorts, in all of which patients kept a diary of GI symptoms, food intake, and, optionally, psychological distress and exercise, either using the app *mySymptoms* (screenshot in Figure 26), a MS Excel template, or a pen & paper template.



Friday 22 March (example)			
Time	Food intake	Bloating	[Symptom]
00:00-00:59		0	
01:00-01:59		0	
02:00-02:59		0	
03:00-03:59		0	
04:00-04:59		0	
05:00-05:59		0	
06:00-06:59		2	
07:00-07:59	2 slices of bread (1 ham, 1 cheese, both butter), 1 cup coffee	3	
08:00-08:59		2	
09:00-09:59		1	
10:00-10:59		0	
11:00-11:59		0	
12:00-12:59	1 caesarean salad, 1 glass sparkling water	0	
13:00-13:59		0	
14:00-14:59		4	
15:00-15:59		6	
16:00-16:59		5	
17:00-17:59	1 portion mushrooms, 1 portion potatoes	4	
18:00-18:59	1 cup of coffee with milk and sugar	8	
19:00-19:59		5	
20:00-20:59		2	
21:00-21:59	1 glass red wine	1	
22:00-22:59		0	
23:00-23:59		0	

Figure 26: Screenshot of the app mySymptoms (left) and the pen & paper template (right).

The sole inclusion criterion was the presence of bothersome GI symptoms more than once a week. Recruitment procedures and study methodology per cohort are given in Table 11. Participants in cohort 1 were required to fill out an online questionnaire with the Rome IV[13] questions that define IBS and functional dyspepsia (FD, epigastric pain syndrome, EPS, and postprandial distress syndrome PDS), as well as the IBS severity scoring system (IBS-SSS, scale: 0-500[14]), the visceral sensitivity index (VSI, scale: 0-75[15]) for GI-specific anxiety, the food subscale of IBS quality of life (IBS-QoL, scale: 0-100[16]), and questions about perceived triggers. We also queried age and sex, and which GI symptoms participants had more than once a week. Participants in cohort 2 had a short oral interview where their GI symptoms and trigger perceptions were discussed. The reason for launching three cohorts rather than one was to be able to build up experience in study design.

Table 11: Cohort characteristics.

	Cohort 1	Cohort 2	Cohort 3
N (enrolment)	50	28	174
N (adequate diary)	20	26	163
Location	The Netherlands	Sweden	International (app)
Participating centres	Maastricht University, KU Leuven, University of Gothenburg	University of Gothenburg	KU Leuven, University of Gothenburg
Year of data collection	2019	2017	2018
Recruitment	IBS magazine, Twitter, Facebook, website of patient society	Flyers in university and health care sites, student website	Opt-in within app
Diary length criterion	≥ 3 weeks	≥ 2 weeks	≥ 3 weeks
Diary platform	*mySymptoms* app, pen and paper, MS Excel template (free choice)	*mySymptoms* app, pen and paper, MS Excel template (free choice)	*mySymptoms* app
Questionnaires	Rome IV, IBS-SSS, VSI, IBS-QOL, symptoms, trigger perceptions	Oral interview about symptoms and trigger perceptions	None
Incentive	Personalised results	Two cinema tickets	None (anonymous)
Informed consent	At enrolment	At enrolment	*A posteriori*
Ethics committee	Maastricht University, the Netherlands	Regional ethical review board, Gothenburg, Sweden	KU Leuven, Belgium
Ethics permission	Exemption granted	Held	Deemed unnecessary

The procedure of keeping a diary via *mySymptoms* has been detailed previously[1]. The pen and paper and MS Excel templates had 24 rows per day, i.e. one per hour, where participants could write down food intake in free text, and symptoms on a scale from 0 to 10. Data pre-processing was done as described previously[1], although the minimum number of food reports per day was lifted from 2 to 3 (i.e. stricter quality control). Furthermore, reported Bristol stool forms 5, 6, and 7 in the absence of a diarrhoea entry were arbitrarily recoded to diarrhoea scores 2, 6, and 10 (following the default scale of 0 to 10).

Internal validation of trigger identification algorithm

The trigger identification algorithm has been described previously[1], and was run in R version 3.5.3[17]. However, the time to symptom onset was not fixed at 8 hours, but at 2 hours for abdominal pain, belching, and diarrhoea, 4 hours for bloating, nausea/vomiting, heartburn, discomfort, headache, and psychological distress, and 8 hours for flatulence and somatic symptoms. These choices were based on food challenge studies (e.g. [18, 19]), as well as a practical trade-off between capturing most lifestyle-related symptoms while limiting background noise.

For validation purposes, we split each diary into training data (first half) and test data (latter half). The cut-point was halfway, although diaries shorter than 20 days were excluded because further splitting would render unreliable results, and diaries longer than 8 weeks were always split at 4 weeks because in clinical practice, patients should not be requested to keep a diary longer than that. In both the training data and test data, we extracted 'trigger scores' per food product per symptom as previously described[1], and also for psychological distress and exercise if reported. Trigger scores were made to follow a standard z-distribution. We then built a linear model to predict the trigger scores in the test data, using 34 engineered predictor variables (one predictor was the trigger score in the training data, the full list is given in Table 12).

Table 12: 34 predictors of the trigger scores in the test data.

Category	Features (training data only)
Symptom dummies	Bloating/flatulence, pain/heartburn, nausea/vomiting, diarrhoea, headache/psychological distress, somatic
Lifestyle dummies	Event frequency, nighttime event, high protein, high fat, high carbohydrate, grain products, FODMAP products, sugary products, stimuli, healthy products
Symptom features	Event count, % in morning, % in evening, % at night
Lifestyle features	Item count, food reporting density level, food reporting density slope, item frequency, item consistency between days, item consistency within days, co-consumption with other items, co-consumption with top-3 triggers excluding itself
Lifestyle-symptom association features	% of items with association of $p<0.5$, association consistency, trigger score, trigger score p-value, symptom severity in week of lowest exposure to item, symptom severity in week of highest exposure to item

The correlation between predicted and observed trigger scores in the test data was stratified by the global food/stress/symptom association (as previously described[1]). Observed trigger scores were binned into 50-tiles of predicted trigger scores, and, for each n-tile, we extracted the percentage of observed trigger scores larger than minus smaller than 0. This percentage was used as the confidence of a given item being a true symptom trigger.

Further validation was sought according to the following line of thought. Ultimately, if a patient were to be given lifestyle advice, the patient would be asked to exclude the top-5 triggers for a certain period, and his/her symptom severity in that period would define the effect of the advice. The present study, however, did not include a controlled follow-up with trigger exclusions. As an alternative, we extracted the top-5 triggers from the training data, and determined the period in the test data in which the exposure to these items was the lowest, i.e. mimicking the scenario of a lifestyle advice, yet free from placebo effects. To this end, exposure to the top-5 triggers in the test data was summed dynamically over a period of 7 days (example in Figure 27). We then determined the symptom severity in the period of lowest exposure to the triggers, and computed a p-value by

simulation with 10,000 iterations under the null-hypothesis (symptom severity not reduced in the period of lowest exposure to triggers).

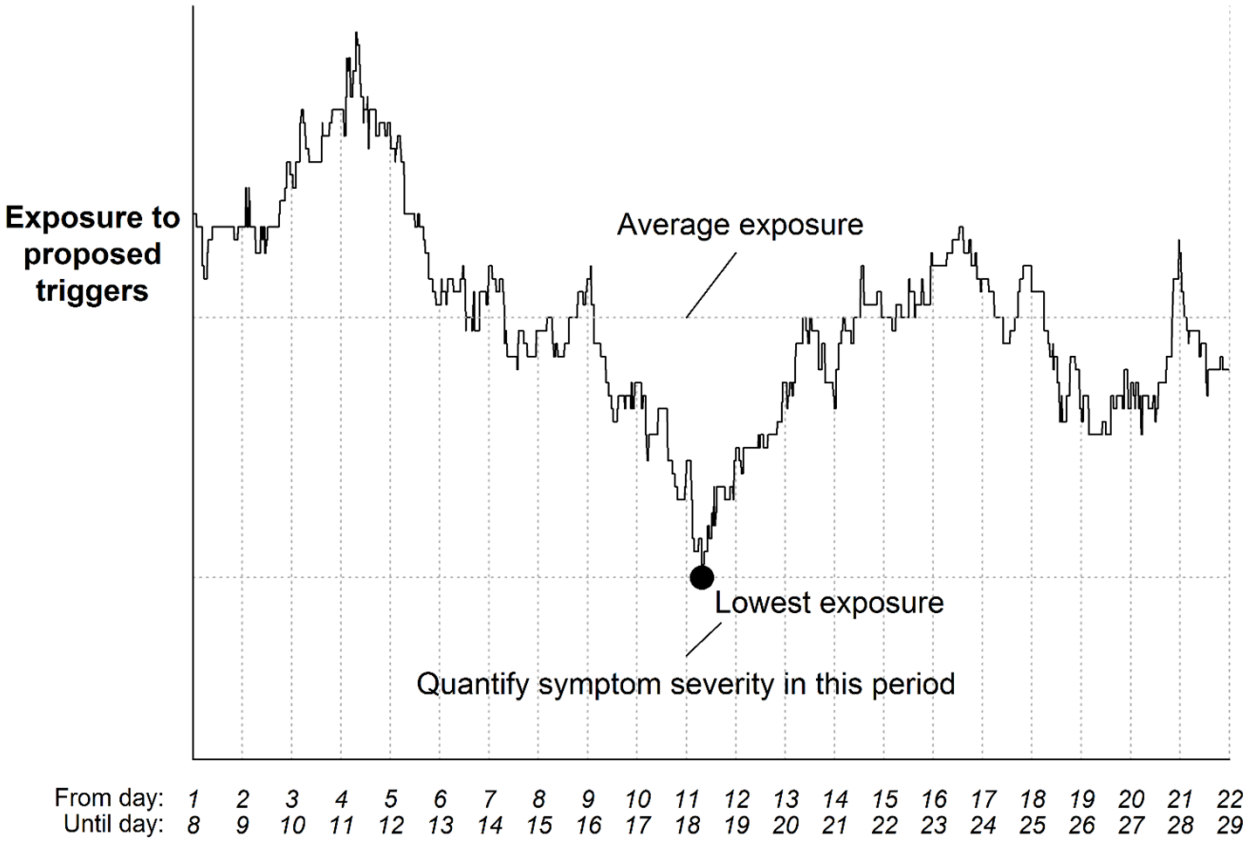


Figure 27: Example of dynamically summed exposure to the top-5 of triggers.

A key bias to the resulting p-values is the reporting density. For example, it can happen that a participant usually reports 10 times a day, but also has a period with only 5 reports a day, because of distraction or fatigue with the study protocol. In that case, the period of 5 reports a day is likely to be the week of lowest trigger exposure, and is also likely to have a reduced symptom severity, simply because the person reported less in general. We adjusted for this bias by simulation, with 10,000 times a random set of n=5 items taken as triggers to generate a null-distribution. Food reporting densities (number of food report occasions per day) of the first 28 days were analysed as latent class mixed model (R-package *lcmm*[20]).

The exact same procedure was performed for high FODMAP foods as well as for foods part of a processed diet. The foods labelled as high FODMAP or processed are listed in Table 13.

Table 13: Items considered to be high in FODMAPs or part of a processed diet.

High FODMAP items	Apple, bread, bread and cereals, breakfast cereals, cabbage, candy bars, cereal products, chocolate, chocolate milk, confectionery, fruits such as melon mango or pineapple, ice-cream, jam, legumes, onions, peas, pizza, pizza and savoury pastry products, salty snacks, savoury pastries, soda pop light, sugary products, sweet bakery, sweet pastries, sweet spreads, sweetened beverages, sweets, vegetables such as broccoli cauliflower or eggplant
Items part of a processed diet	Aged meats, alcoholic beverages, alcoholic beverages other than beer or wine, beef, beer, biscuits, candy bars, chips (fries), chocolate, chocolate milk, confectionery, deep fried products, fatty sauces, ice-cream, jam, meat, meats, night-time intake, pizza, pizza and savoury pastry products, pork, salty snacks, savoury pastries, soda pop, soda pop light, sugar and honey, sugary products, sweet bakery, sweet pastries, sweet spreads, sweetened beverages, sweets, wine

Meta-analysis of common symptom triggers

We performed a meta-analysis on the full diaries of all participants, in order to establish the most common triggers for GI symptoms. This was done, per symptom, for all reported food items, psychological distress, exercise, and also all other symptoms. The outcome was the prospective increase in symptom severity after exposure to a trigger, adjusted for reverse causation, time of the day, and lifestyle changes as described previously[1]. We performed random effects meta-analyses using the R-package *meta*[21] to allow for heterogeneity of effects. Analysis confined to the four most common symptoms to conserve power (i.e. abdominal pain, diarrhoea, bloating, and flatulence).

Results

Cohort 1 consisted of 50 participants, of whom 74% had IBS according to Rome IV, and 42% had FD. Most had abdominal pain, flatulence, bloating, diarrhoea, or discomfort not covered by another symptom term in table 14. Participants had a median IBS-SSS score of 305. i.e. moderate to severe IBS. Descriptive statistics can be viewed in Table 14, and the relations between variables are given in Figure 28.

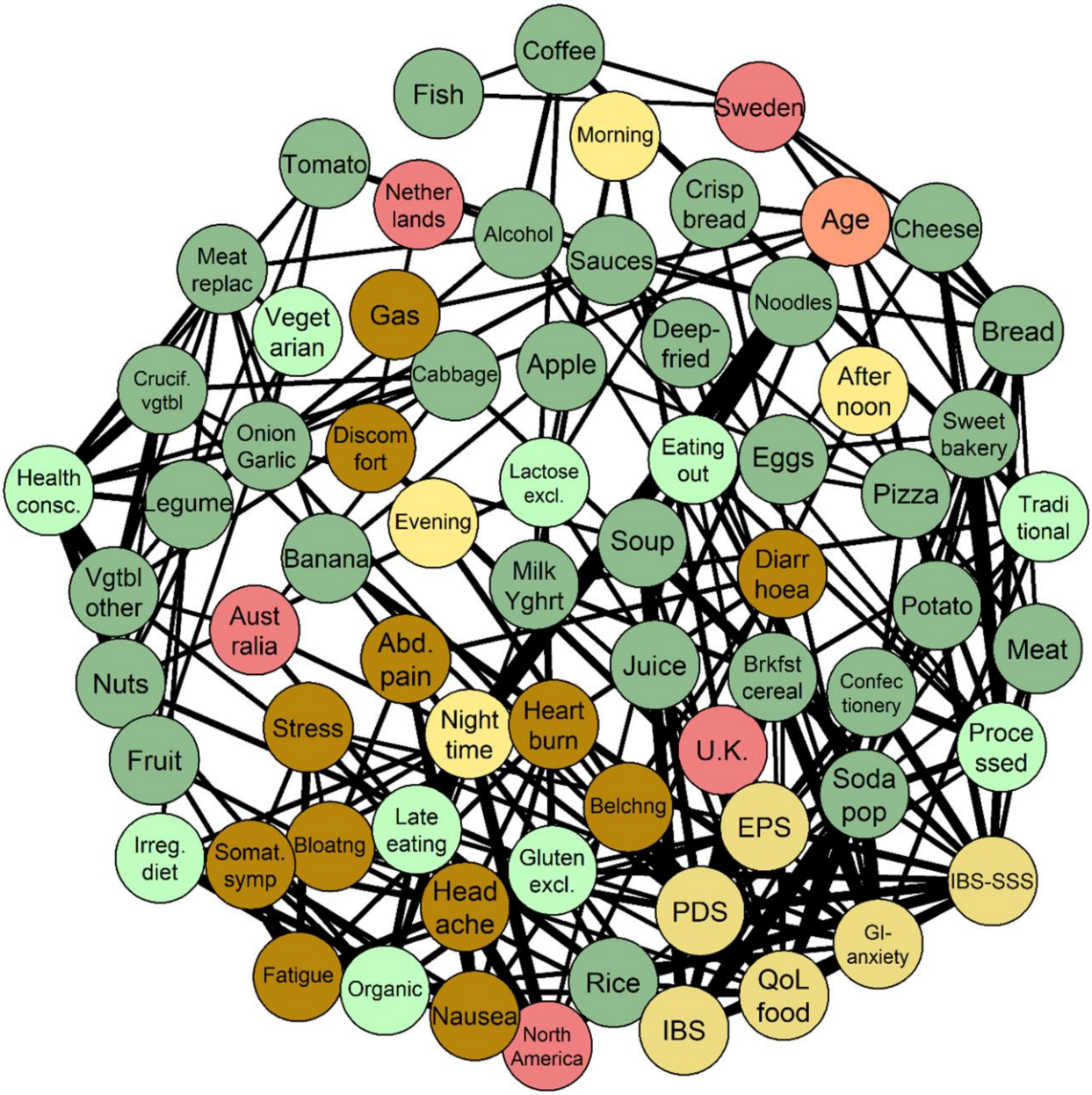


Figure 28: Correlation network of symptom and food features in the present study.

As for participants' perceptions about triggers, psychological distress topped the list with 64%, followed by food products sweet bakery/confectionery (52%), bread/pasta/rice, milk/cheese, and fats/oils/sauces (all 46%), legumes (44%), fruit (30%), vegetables (22%), meat/fish/eggs (16%), and potatoes (4%). Cohorts 2 was a roughly even mix of patients with IBS and subthreshold-IBS GI symptoms, as concluded from oral interviews. Cohort 3 was anonymous and not characterised.

Table 14: Descriptive statistics of cohort 1. Values are percentages or medians [interquartile range]. N.O.S.: not otherwise specified.

Descriptive	**n=50**	**Symptom > 1/week**	**n=50**
Female	98%	Abdominal pain	88%
Rome IV – IBS	74%	Flatulence	80%
Rome IV – FD	42%	Bloating	74%
PDS	34%	Discomfort N.O.S.	56%
EPS	20%	Diarrhoea	54%
Age (years)	45 [32-54]	Nausea	36%
IBS-SSS	305 [240-330]	Excessive belching	24%
GI-specific anxiety	42 [31-49]	Heartburn	20%
IBS-QoL food	58 [42-83]	Vomiting	6%

The number of diaries we received was 20, 28, and 174 for the three cohorts respectively (cohort descriptions in table 11). Cohort 1 had had 30 individuals drop out of the study (silently, i.e. no reasons were given), and 13 diaries (2 from cohort 2, 11 from cohort 3) did not pass quality control, because either food or symptoms were not recorded.

The vast majority of participants reported around 5 times a day, and this was stable over time. Approximately 9% of individuals reported with a larger frequency, but here, too, reporting density was quite stable for most participants (Figure 29).

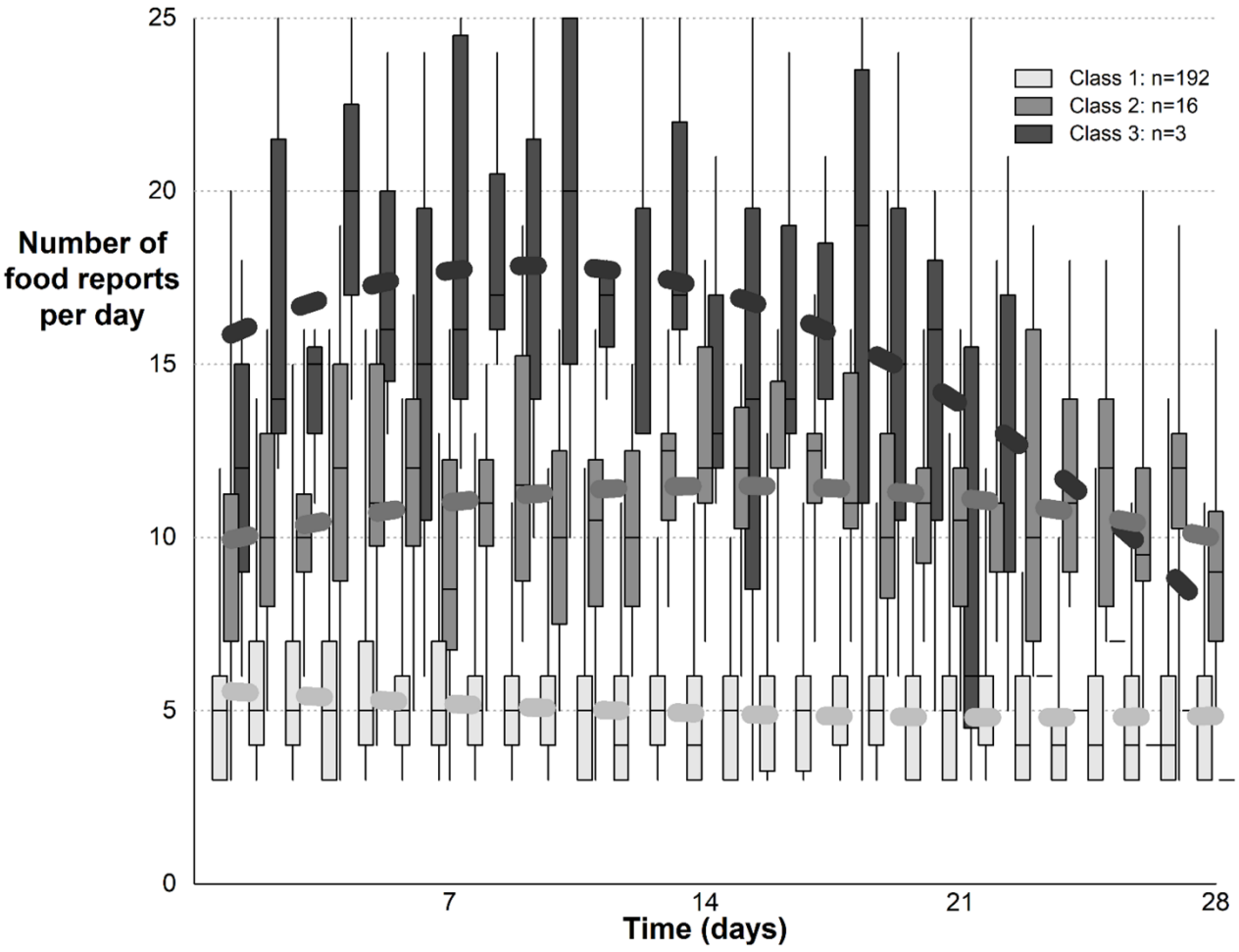


Figure 29: Food reporting density shown as latent class mixed model.

Internal validation of trigger identification algorithm

Of the 209 diaries that passed quality control, 163 were long enough to split into training and test data (19, 10, and 134 for the three cohorts, respectively). We studied a total of 501 symptoms and 12,946 possible triggers. Predicted and observed trigger scores in the test data were correlated ($r=0.27$, $p<0.001$), and this correlation interacted with the strength of the global food/stress/symptom association. Of the 501 symptoms, 42 (8%) had a strong global food/stress/symptom association ($p<0.01$), and here trigger scores were best predicted ($r=0.45$, $p<0.001$). Another 42 (8%) had a global association of extent $0.01 \leq p < 0.05$, and here the correlation was $r=0.38$, $p<0.001$. Weaker food/stress/symptom associations led to smaller correlations between predicted and observed trigger scores in the test data (Figure 30). Trigger confidence was 50% or more for 1 in 28 items, i.e. 1 item per symptom per person on average.

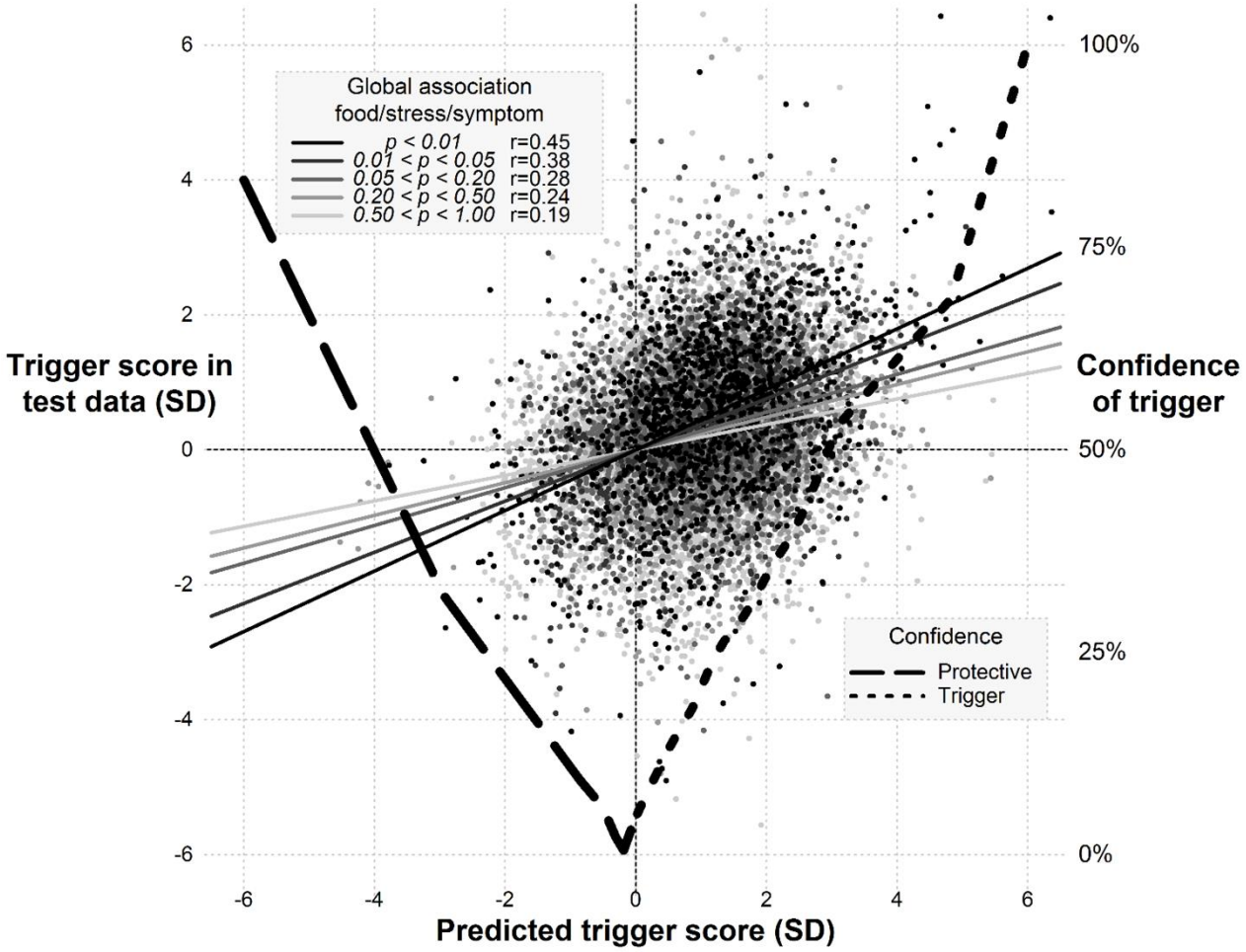


Figure 30: Correlation between predicted and observed trigger scores in test data, stratified by the global food/stress/symptom association (primary y-axis). Dotted / dashed lines: confidence that an item is a trigger (secondary y-axis).

We went on to analyse whether, in the test data, in the week of lowest exposure to the top-5 triggers, symptom severity was reduced. This is a prerequisite for the future success of keeping a diary in clinical practice. Symptoms in the week of lowest trigger exposure were reduced in 62% of cases ($p<0.001$). After adjustment for reporting density, a statistically significant effect remained ($p=0.043$). Symptoms in the week of lowest FODMAP intake were reduced as well, although less strongly so in the adjusted model ($p=0.099$). Low consumption of processed foods was not associated with an improved symptom severity after adjustment for reporting density ($p=0.458$). Results can be viewed in Figure 31.

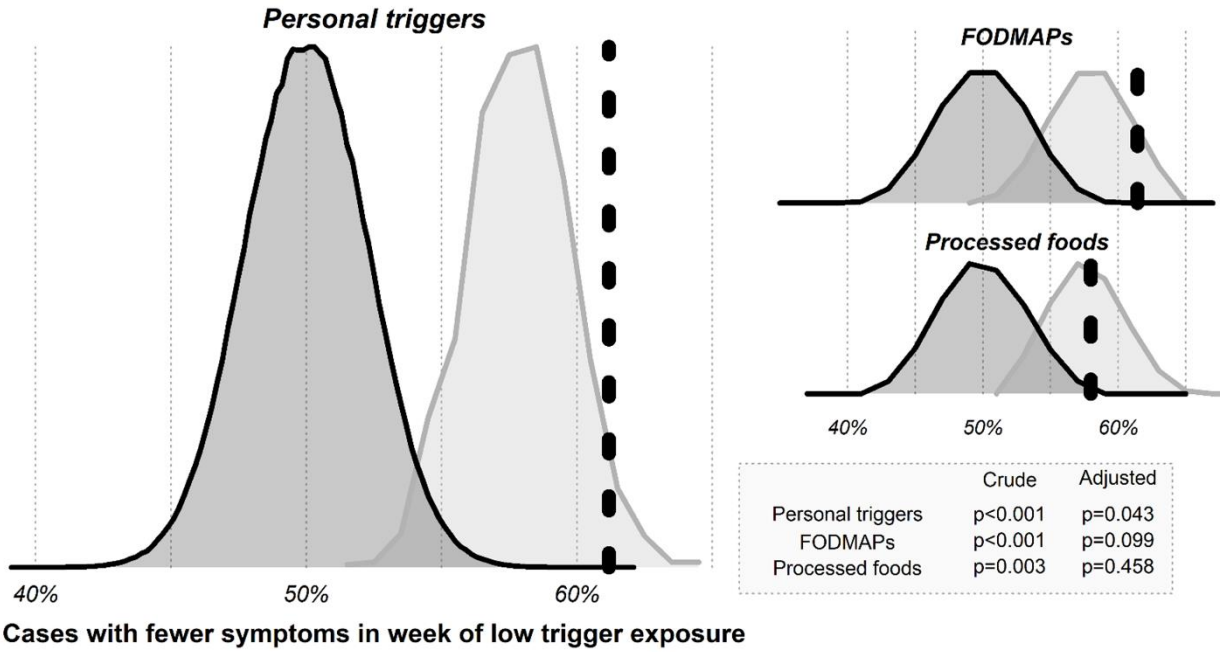


Figure 31: Percentage of cases with improved symptoms in the week of low exposure to the top-5 of triggers (thick dashed line), and its relation to the null-hypothesis adjusted (light grey curve) and unadjusted (dark grey curve) for reporting density. The same is shown for the weeks of low intake of FODMAPs and processed foods respectively.

Meta-analysis of common symptom triggers

Figure 32 shows, for each symptom, meta-analytic estimates for the top-5 (group-level) triggers, the bottom-3 (negative association), and some selected items. Caloric intake late in the evening or at night seemed to be an important trigger for bloating ($p<0.001$), abdominal pain ($p<0.001$), and flatulence ($p=0.006$). Rice and bread triggered abdominal pain ($p=0.006$ and 0.02). Diarrhoea was predicted by the intake of confectionery, coffee, and spices in particular (all $p<0.001$), whereas flatulence was often triggered by the intake of fruits ($p=0.008$), onions, and bread (both $p=0.009$). Psychological distress was not predictive of an increase in GI symptoms, at least not after adjusting for reverse causation (GI symptoms may increase psychological distress). Exercise weakly predicted a decrease in abdominal pain ($p=0.027$). An event of diarrhoea predicted a decrease in other GI symptoms, especially flatulence, whereas flatulence often preceded diarrhoea (both $p<0.001$). Other associations of interest were that coffee reduced discomfort and fatigue whereas onions increased both of these, and alcohol reduced psychological distress but increased heartburn (all $p<0.05$).

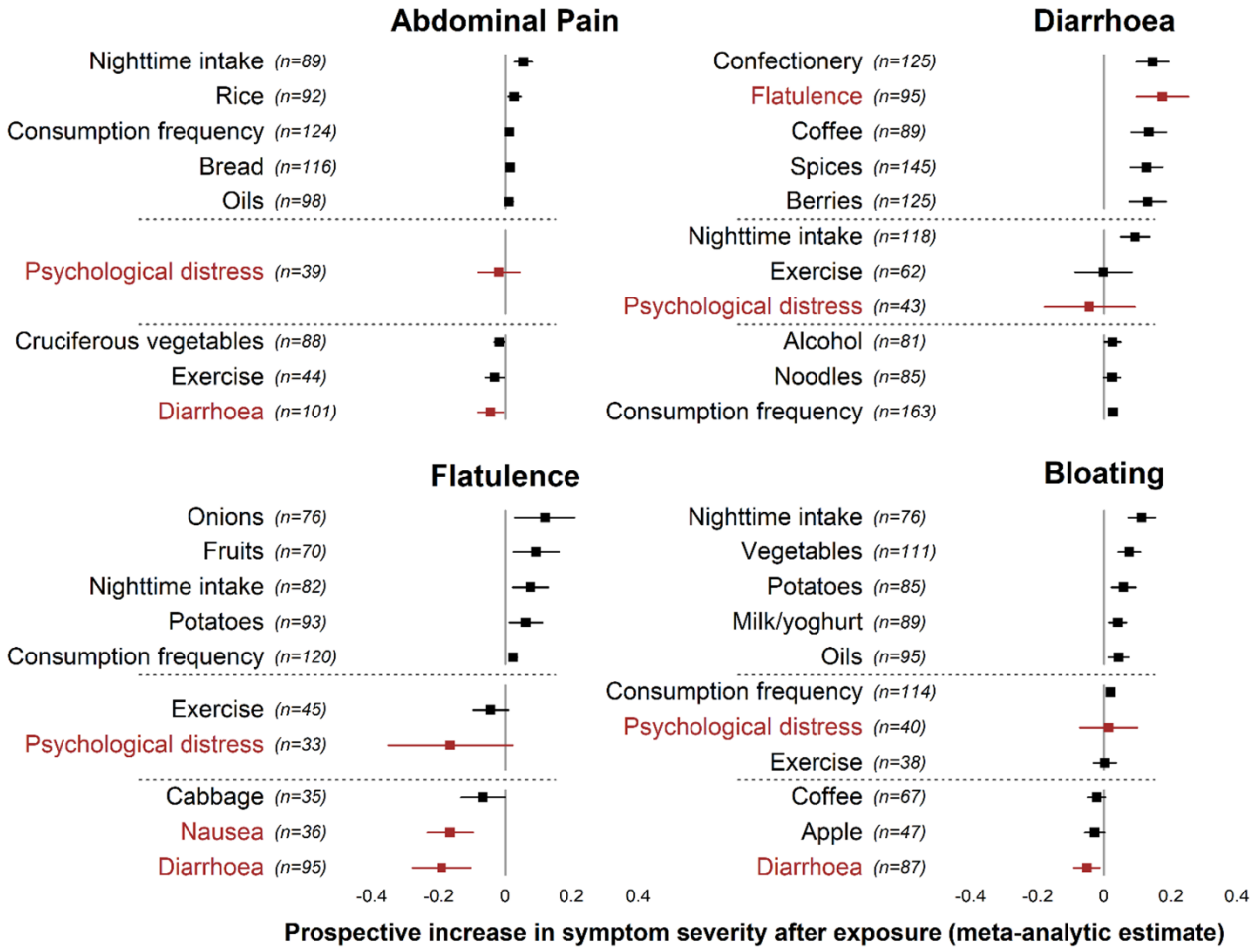


Figure 32: Meta-analysis of triggers for four common GI symptoms. The top-5 is sorted by the lower confidence limit; the bottom-3 is sorted by the upper confidence limit. N-values are the number of participants who reported the respective item as well as the respective symptom.

Discussion

This study shows that keeping a diary of food intake, psychological distress, and GI symptoms can identify personal GI symptom triggers, especially when a global association between food, stress, and GI symptoms is established. Furthermore, in the period when the participant naïvely had low exposure to the triggers, symptom severity was reduced. Finally, we show in a meta-analysis that caloric intake late in the evening or at night may be an important trigger for bloating and other GI symptoms. Furthermore, specific food-symptom associations were found, e.g. for abdominal pain (rice, bread), diarrhoea (confectionery, coffee, spices), flatulence (onions, fruits), and bloating (vegetables).

Personalised management of GI symptoms

A conceivably important goal in the management of GI symptoms, a health problem with heterogeneous underlying pathophysiology, is to personalise the advice given to patients. When done properly, this can resolve the problem of between-person heterogeneity of mechanisms and treatment responses, and it is also an additional resource on top of the current strategies. Personalised management can be achieved in several ways. One of these is to keep a diary on a smartphone. Many digital applications exist for GI purposes[22], but the quality of their output is typically not verified and/or not published. The present validation study highlights that the advice can be repeatable and meaningful. Moreover, the period when exposure to the top-5 triggers was low tended to coincide with a period of reduced symptom severity. Our diary analysis service can therefore be considered to be capable of giving meaningful personalised lifestyle advice to at least subsets of patients. At the same time, much unexplained variance persists, which will be largely due to reporting inaccuracy, response shift, and unreported factors relevant for GI symptoms. Some participants commented that their internal standards had changed throughout the study, and wanted to restart the diary anew. A fantastic opportunity to improve reporting accuracy and consistency is to use microelectronics / smart devices to track changes in physiology, as these measure objectively and with accurate timestamps. A first step in their application would be to select physiologic outcomes most reflective of symptoms or disturbed homeostasis. Candidates would be GI motility, pressure, acidity, heart rate, continuous measurement of abdominal girth as direct measure of abdominal distension, or interactions of these. The second step would then be to dynamically assess the person-specific effects of different food items / stress conditions on physiology, which could serve as the basis for personalised lifestyle advice in IBS. We hope that the present study can inspire such efforts.

All of that said, other roads to personalised management of GI symptoms have been paved. Fritscher-Ravens *et al*[23] injected food allergens in controlled conditions, and used confocal laser endomicroscopy to record losses of epithelial integrity and infiltration by immune cells. Such adverse reactions were seen in 61% of IBS patients but 0% of non-IBS controls. Replication is warranted, especially through studies that subsequently give personalised advice to exclude the identified allergens. Responses to the low FODMAP diet can be predicted using volatile organic compounds in faeces[24] or the microbiota[25]. It would be interesting to see whether biomarkers can also predict specific food intolerances as identified by a diary or endomicroscopy.

Lifestyle triggers on the group level

We present evidence for several food items and eating habits as triggers for GI symptoms. Caloric intake late in the evening and at night was associated with bloating in particular. This is in line with a study by Gill *et al*[26], who restricted daily eating intervals of participants from >14 hours to 10-11 hours and reported beneficial effects on general health at 16 weeks. However, studies specific to GI symptoms are missing, and it remains unclear what part of circadian metabolism might be at play in GI symptom generation. Coffee, spices, and confectionery, amongst others, were associated with a subsequent diarrhoeal event. This is in agreement with the NICE guidelines for IBS, which recommend limited consumption of (caffeinated) coffee, spices, and (artificially sweetened) confectionery[5]. In our study, though, we lacked the information to consistently distinguish between caffeinated and non-caffeinated coffee, or between sugar-sweetened and artificially sweetened items. Psychological distress was not meta-analytically associated with a subsequent increase in GI symptoms in our cohorts, because the reverse association was as strong or stronger (flatulence). In some individuals psychological distress had a larger trigger score than any food item. While mechanistic studies suggest that psychological distress is capable of changing GI physiology (e.g. disruption of the intestinal barrier[27]), other studies found only a weak influence of daily stress or state anxiety on GI symptoms[28, 29]. Possible explanations for this discrepancy are a difference in definition of psychological distress, or that self-reports differ from psychological distress as induced in controlled designs and measured through markers such as cortisol. Finally, we show that diarrhoea improves abdominal pain in the subsequent 2 hours, which supports the Rome conceptualisation of abdominal pain related to (and usually improved by) defecation[30].

This study presents an objective quantification of relations between food intake, psychological distress, and GI symptoms. This was done in three cohorts, of which one was well-characterised. A strength of our analysis algorithm is that it is highly flexible (can process multilingual free text, any diary length, can toggle between food items and food groups, and does not require portion sizes), and that it adjusts for important confounders: reverse causation, time of the day, lifestyle changes[1], and, to some degree, response shift. A strength of the validation analysis is that we tested symptom severity in a period of low exposure to the triggers, which mimics an intervention whilst remaining clear of placebo effects. Limitations of our study include reporting inaccuracy and residual response shift. Besides, the incentive of personalised results in cohort 1 did not prevent a high drop-out rate (60%), while, apparently, monetary or tangible incentives such as in cohort 2 are needed. A follow-

up phase with trigger exclusions was not in scope of the present study, but could be a next step. Finally, our study would have been stronger with broader characterisation of participants, and if we had included objective biomarkers in the design. These limitations should be addressed in follow-up studies.

In conclusion, keeping a diary of food intake, psychological distress, and GI symptoms can identify personal GI symptom triggers for at least some patients. Common triggers for GI symptoms are in line with the NICE guidelines[5], and add that caloric intake in the late evening and at night may increase GI symptoms. The diary approach of the present study can help pave the way towards personalised management of GI symptoms in patients with IBS and other functional GI disorders.

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GENERAL DISCUSSION

Overview of results

The title of this work is '*Symptom patterns in IBS*'. Symptom patterns were studied on various levels, ranging from diagnostics to a (potential) treatment strategy:

- Diagnostics of IBS and its validation as separate disease entity (study 1);
- Epidemiology of IBS and comorbidity patterns (study 2);
- Development of IBS over 5 years, and the role of psychological features (study 3);
- Mechanisms driving short-term GI symptoms, i.e. food and psychological distress (study 4);
- Personalised treatment for GI symptoms, based on a food/symptom diary (study 5).

Results of the 5 studies underline the heterogeneous nature of IBS. When managing an IBS patient, it is important to consider her/his comorbidities, such as overlapping GI disorders and anxiety disorders. GI-specific anxiety, where present, may be targeted using cognitive behavioural therapy and this could lead to symptom improvement. Food intolerances are common (but not ubiquitous) in IBS, and may be identified using a food-symptom diary, provided that it is analysed with a good algorithm. An overview of conclusions is given in Figure 33.

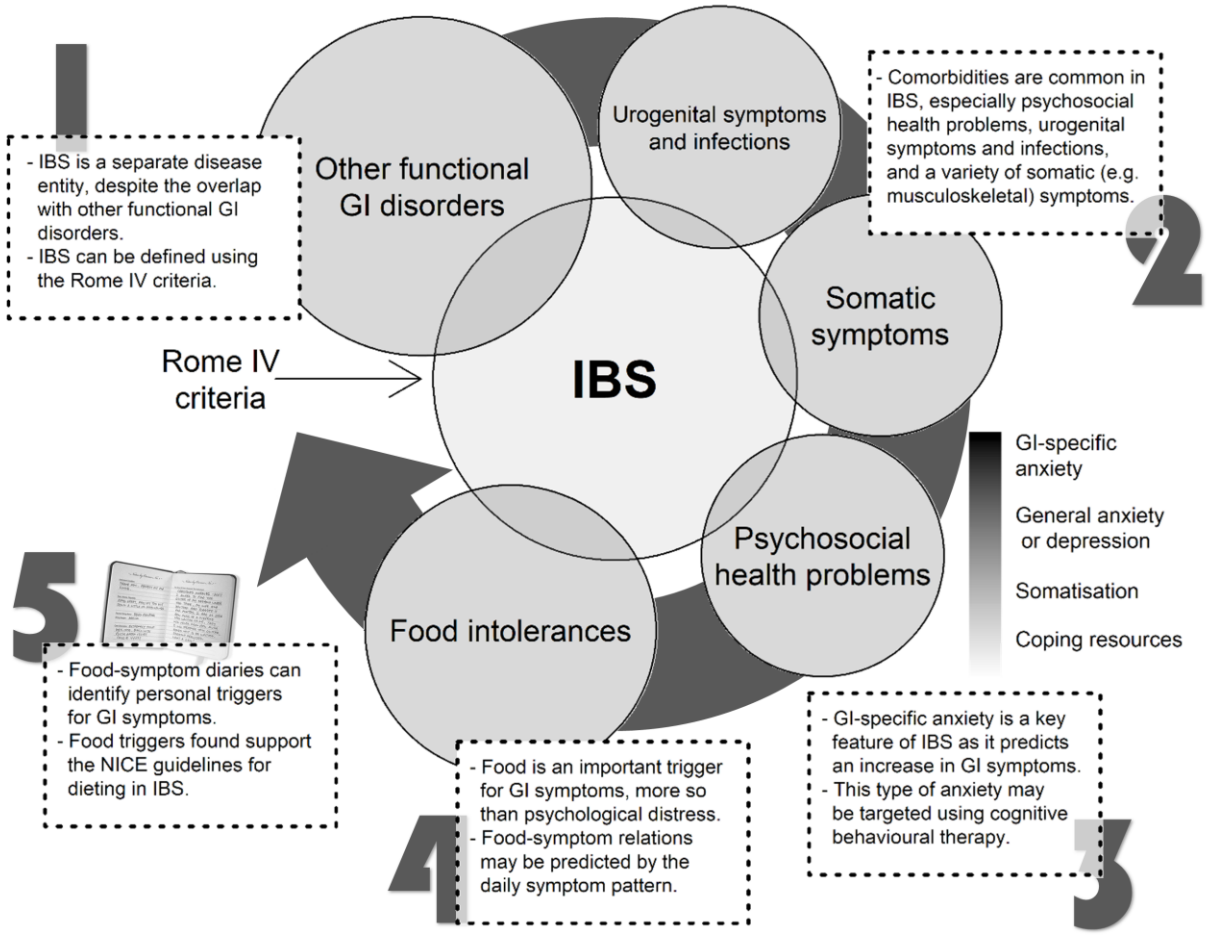

Figure 33: Simple overview of conclusions drawn from the 5 studies in this thesis.

Positioning in the field

IBS research has witnessed several trends and paradigm shifts. IBS studies in the 1980s made frequent mention of organic GI diseases (figure 34), such as in the context of overlap. Gradually, IBS has become better accepted as distinct entity, even from other functional GI disorders. Study 1 of this thesis provides support that IBS is distinct from other disorders such as functional dyspepsia. Management practices have shifted from general advice on fibre intake (1980-1990) to specific diets (e.g. FODMAP diet) in the 2010s, and, relevantly, more and more IBS studies (~3% in 2019) address personalised management. Studies 4 and 5 intend to fuel personalised nutrition in IBS, by providing a well-defined architecture for keeping and analysing diaries, as well as evidence that it can be effective. A roadmap for developing personalised management is presented later in this chapter. Lastly, while IBS cannot be cured, more and more studies address patient quality of life and coping. Study 3 shows that GI-specific anxiety is a key target for improving IBS symptoms and quality of life.

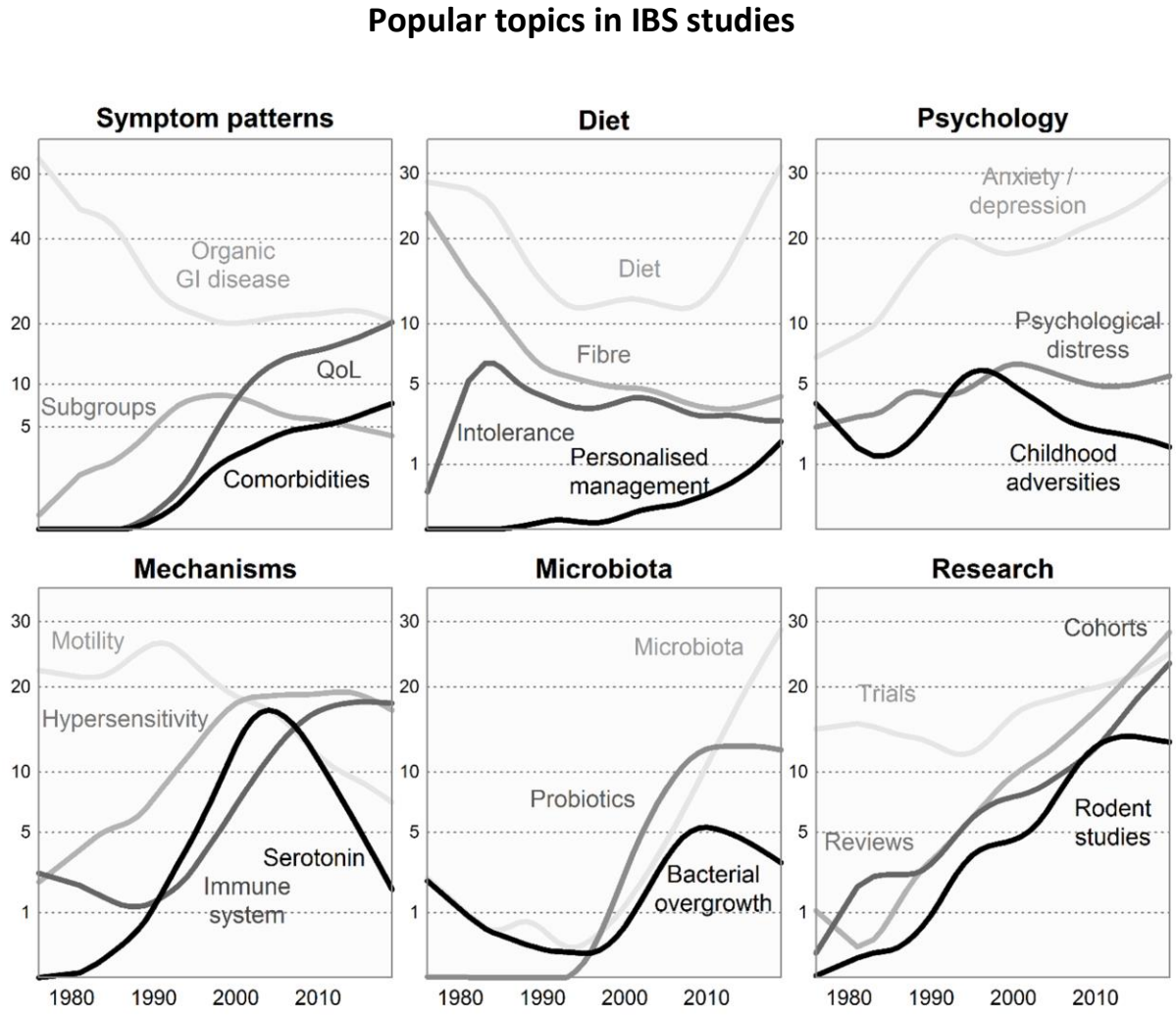

Figure 34: Of 9640 IBS study abstracts, trends in mentions of specific topics. Y-values are %s of articles a year on a square root scale.

Causal inference in symptom pattern research

The 5 studies in this thesis were all observational. A major quality determinant in observational studies is the strength of causative evidence. Two things must be noted. First, causation cannot be demonstrated by any type of research; not even *in vitro* studies or trials. It is rather the failure to falsify a cause-effect relation that makes causation credible. Second, opportunities exist in patient studies to lift correlation towards causation by serial adjustment for various biases (figure 35).

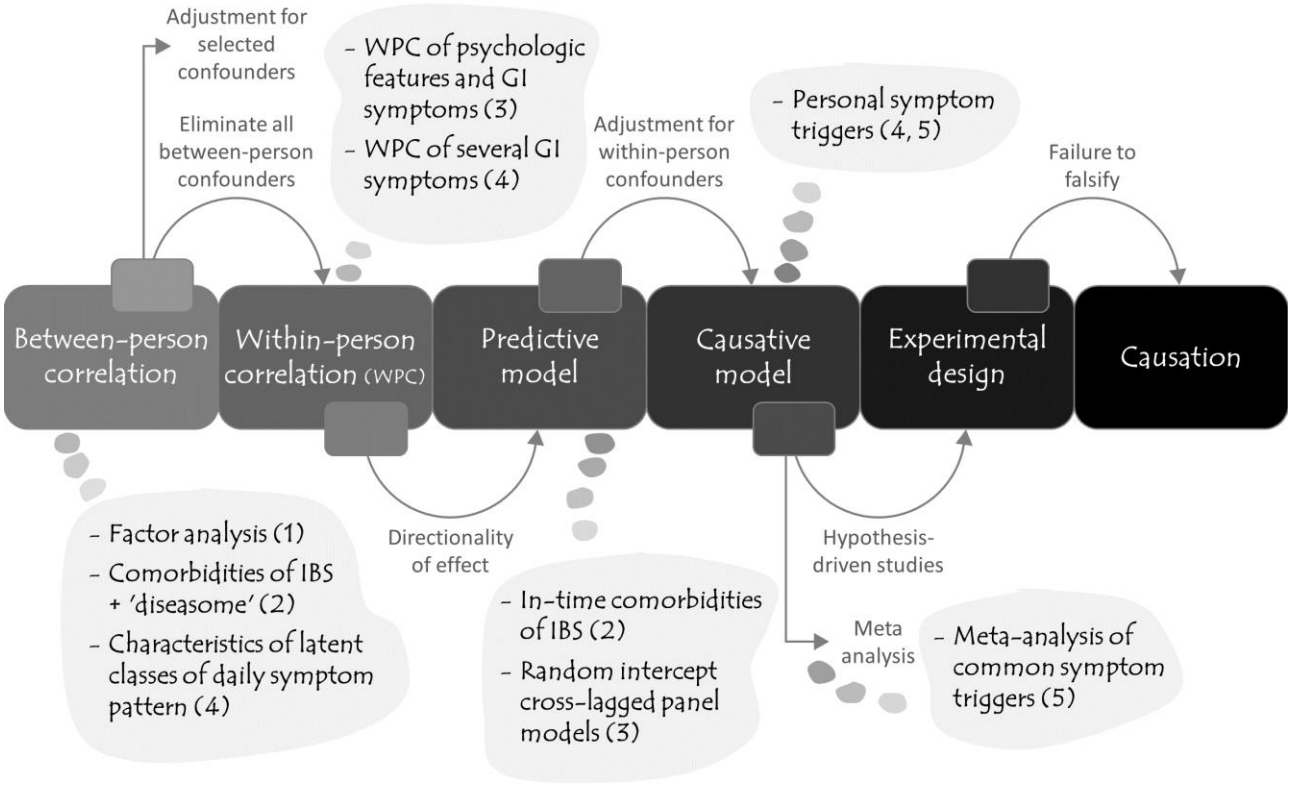

Figure 35: Causality inference in the 5 studies covered in this thesis.

One key bias is confounding. Study 2 adjusted for known confounders (through matched pairs), and studies 3, 4, and 5 also for unmeasured confounders by eliminating interpersonal variation. A second bias is reverse causation. Adjustment for reverse causation is possible if the time-axis has frequent enough data collection. This was done for the cross-lagged panel model of study 3, the incidence of health problems following an IBS diagnosis in study 2, and the entire studies 4 and 5. Studies 4 and 5 additionally adjusted for within-person confounders (time of the day, long term lifestyle changes). Finally, study 5 boosted its power by meta-analysis of symptom triggers.
Residual biases of all studies include misreporting (discussed in the respective articles) and violation of statistical assumptions where applicable. To conclude, best efforts were made to lift the strength of causative evidence from correlation towards causation, but certain biases remain.

Directions of IBS research

Most of today's research is done on the group level. Studies sample participants, find an outcome, and extrapolate this to a larger population (Figure 36). However, group-level research is problematic in heterogeneous disorders such as IBS, because group averages need not capture phenomena in individual patients.

One clever solution is to do subgroup identification analyses on group-level data. In this way, heterogeneity is not a limiting factor, but rather a requirement for reshaping disease management practices. Subgroup analyses require careful tuning of the study design, because measured variables must include the factor defining the subgroups as well as relevant variables to characterise them once formed. It also deserves mention that many statistics-based subgrouping techniques tend to be sensitive to minor deviations from null-distributions, so that reproducibility can be uncertain.

A second solution for heterogeneity is to study the single patient, and generate directly applicable person-specific advice. A prerequisite for individual-level research is thorough validation of the conclusions drawn, e.g. robustness against within-person heterogeneity (Figure 8). Smart electronics such as lab-on-a-chip might ultimately take individual-level research fully to the patient domain. Finally, when done in a larger number of patients, results can be bundled and group-level or subgroup-level analyses become possible as well.

Innovative and effective IBS studies may be designed through the lens of subgroup- or individual-level research. The next section discusses how personalised IBS management can be achieved.

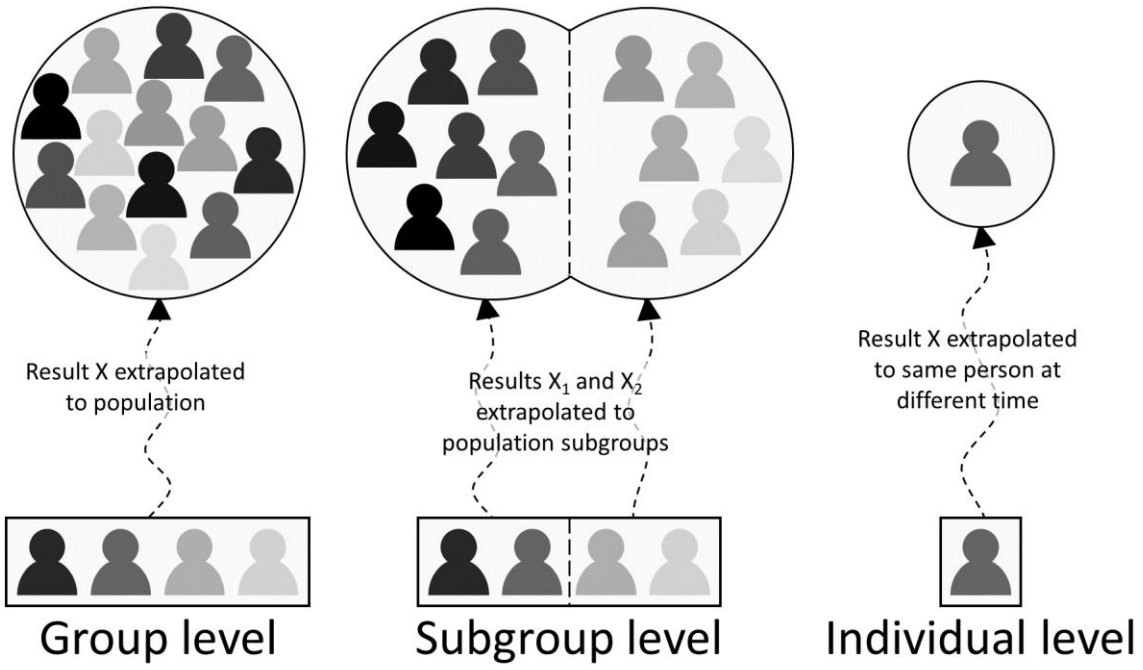

Figure 36: Research on the group level, subgroup level, and individual level (rectangles) lead to different generalisations (circles).

Personalised management of IBS

The 2010s have shaped a novel framework to personalise IBS management. It involves roughly two-to-three parts (figure 37):

- Identification of person-specific lifestyle triggers of GI symptoms (i.e. on the individual level, such that every patient receives personalised advice).
- Identification of predictors of treatment response (i.e. on subgroup level). The result is a new treatment algorithm for IBS, as well as new subgroupings that can change or even replace the definition of IBS.
- Identification of relevant mechanisms. This is a hypothesis-generating endeavour to investigate *why* an IBS patient or patient subgroup might have symptoms. Identified mechanisms can be 'the how' behind trigger-symptom associations, function as predictor of treatment response, or act as surrogate marker for symptom severity.

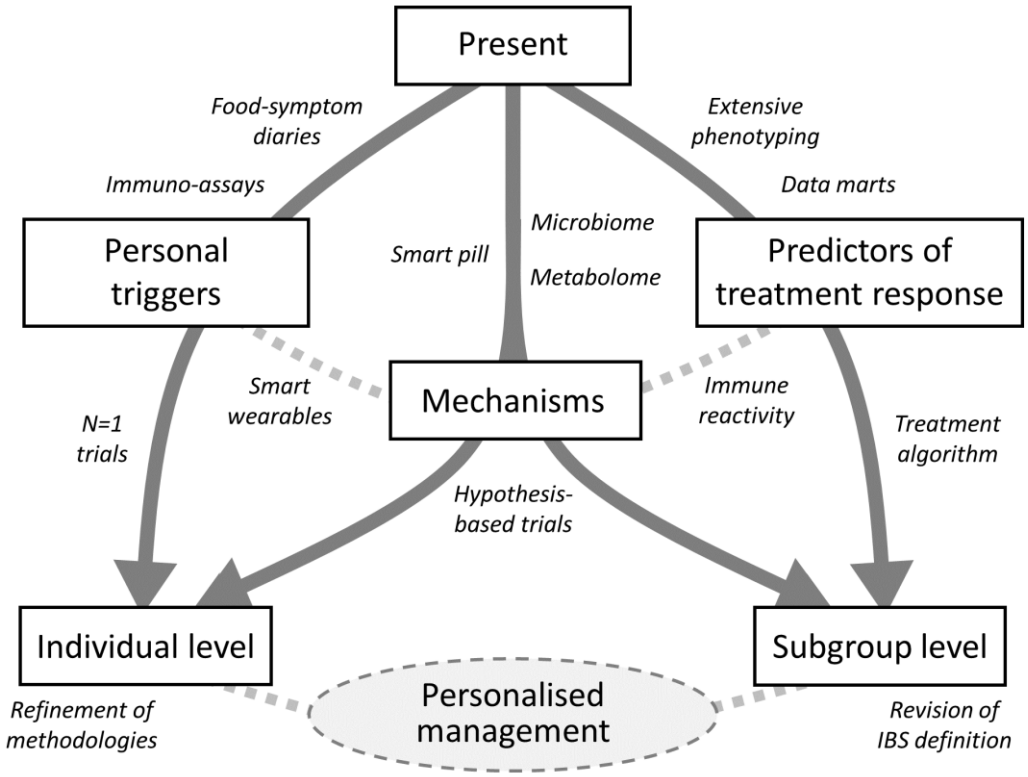

Figure 37: Proposed research framework for personalised management of IBS.

Individual-level and subgroup-level research together shape personalised IBS management (and may also flow into one another). The next sections will discuss the above roads to personalised IBS management in detail.

Personal triggers

Identification of person-specific lifestyle triggers is a three-phase process:

1. Screening phase: lifestyle factors are screened for associations with GI symptoms or pathophysiologic processes.
2. Validation phase: a controlled exclusion of (or exposure to) proposed triggers, and responses in symptom severity are monitored.
3. Refinement phase: the screening methodology is continuously optimised based on the validity.

The screening phase can take several approaches (food/symptom diaries[1,2] analysed with an algorithm, immunoassays[3], or endomicroscopy[4]). An example protocol with food/symptom diaries is given in figure 38, where 2-3 form the screening phase, 4 is the validation phase, and 5 is for refinement of, in this case, the analysis algorithm.

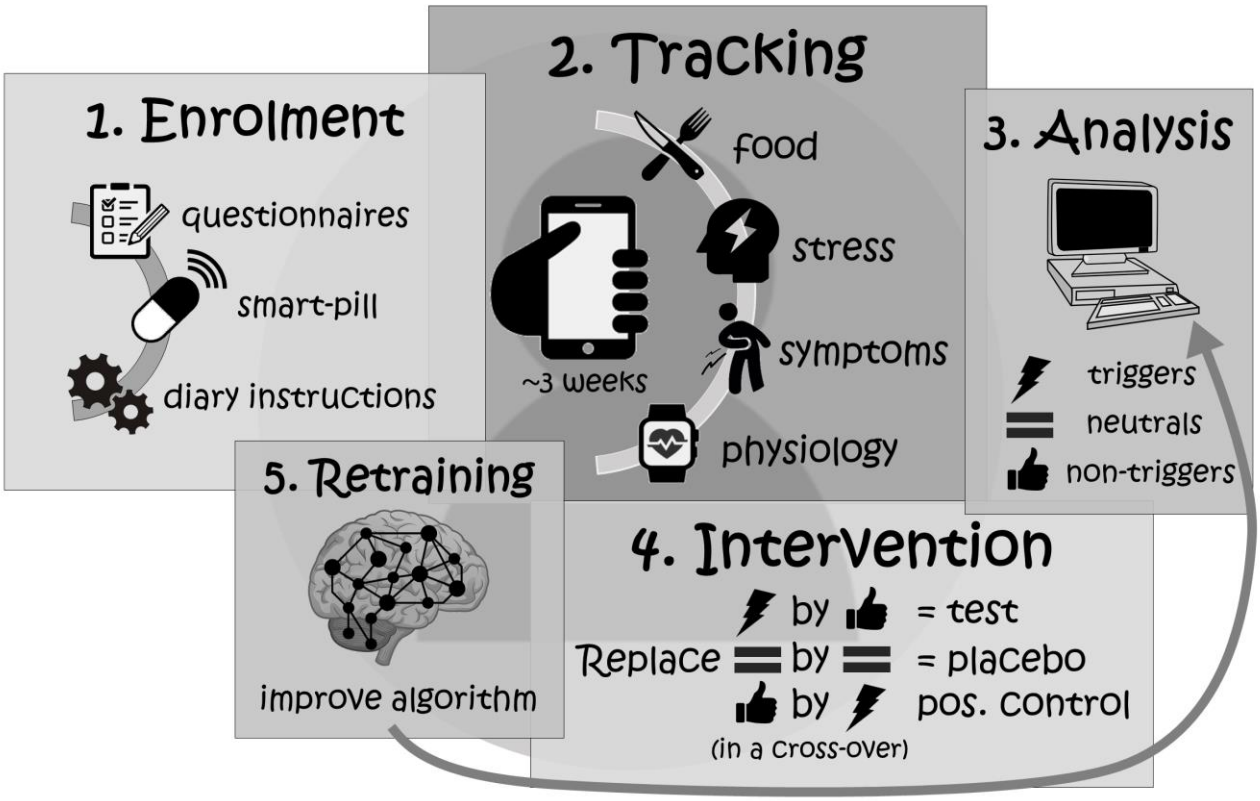

Figure 38: Suggested protocol for identifying personal triggers for GI symptoms in IBS.

Part of the food/symptom diary protocol of figure 38 has been implemented previously[1,2] (tracking of food intake, stress, and GI symptoms, and analysis for triggers). Participant characterisation was thin, and an intervention with follow-up was missing. Both are essential future steps to take the food/symptom diary concept to the clinic.

The food/symptom diary concept provides fantastic opportunities, because it generates a wealth of longitudinal as well as cross-sectional data. Besides pseudo-causal associations between foods (or psychological distress) and GI symptoms, which is the 'core business', one can assay physiologic variables as potential mediators of such associations. Examples are heart rate, skin conductance, and abdominal girth, which can be continuously measured using wearable electronics. Moreover, cross-sectional baseline variables can serve as predictors of a food-symptom or stress-symptom association. Examples are questionnaire data on GI symptom severity, GI-specific anxiety, or food-related quality of life, latent classes of daily symptom pattern[1], but also physiologic information (e.g. the SmartPill[5], which is swallowed and measures for ~1 day the motility, pressure, and acidity in the GI tract). Figure 39 sums up the functionalities of big data tracking studies in IBS research.

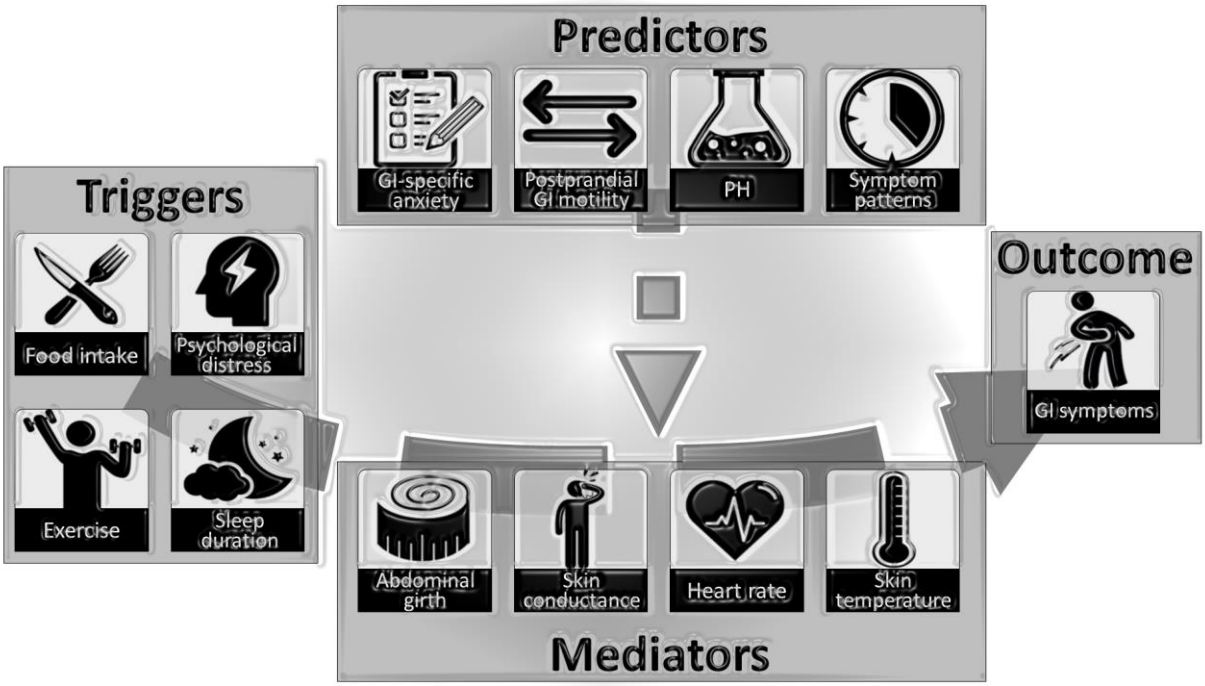

Figure 39: Big data tracking studies in IBS have many functionalities.

Important methodological control points must be built into the protocol. Upon enrolment, patients should receive clear instructions on symptom reporting practices, where symptom severity is ideally rated every hour (or more frequently) on a 10-point scale. Second, the analysis algorithm must adjust for several confounders to approach causality inference. These include reverse causation, long-term lifestyle changes (figure 8, left and middle), and time of the day (figure 8, right). Third, the proposed triggers should be tested in a cross-over-like intervention (e.g. n=1 design), where the top-3 triggers are replaced by 3 non-triggers or vice versa as control condition. Finally, an effective algorithm requires continuous retraining or redesigning based on the results of the intervention.

Predictors of treatment response

Another key need in IBS is an evidence-based treatment algorithm. That is, if a patient has feature X, then treatment A is effective, whereas if the patient has feature Y, then treatment B is effective. A few relevant studies have been done (the microbiota predicted response to FODMAP exclusion[6] and cognitive behavioural therapy[7]), but these considered one treatment only. It takes much data to construe a good treatment algorithm. The following elements are required:

- Several prospective studies covering a number of treatments.
- A decent number of patients per treatment (e.g. n ≥ 100).
- Thorough characterisation of patients.
- A treatment response measure.

It is important to standardise procedures across study centres, as this will allow for data pooling and joint data analysis. Patient characterisation should involve features that can be queried routinely at low cost (e.g. age, sex, IBS duration, IBS subtype, post-infectious IBS status, GI symptom severity, daily symptom pattern, presence of anxiety, and perceptions about triggers). In addition, one may include biomarker assessment (e.g. markers of inflammation, metabolome, or microbiome) or clinical testing (e.g. barostat, manometry, meal challenge, or food-symptom diary). Finally, there should be a single measure of treatment response, such as self-reported adequate symptom relief or the change in IBS-SSS score following treatment.

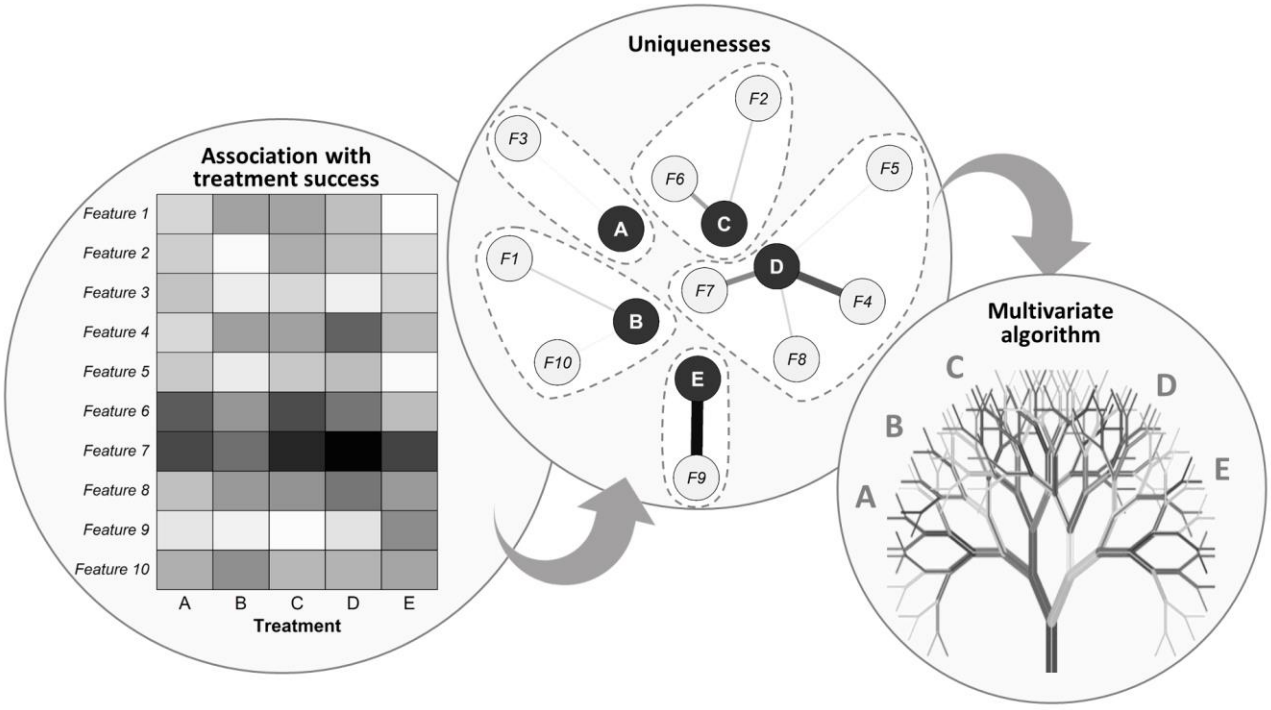

Figure 40: Treatment algorithm applications range from simplistic bivariate designs to complex multivariate trees.

Broad phenotyping of patients in combination with monitoring treatment success provides two key opportunities.

First, provided one includes a sufficient number of patients, it will become possible to build a predictive model that states which treatment is recommendable given the characteristics of a patient (figure 40). Such a model can improve the common trial-and-error-based management of present day, and can be free of cost if one restricts to questionnaire assessment. Another strength is that the model will improve itself once new data comes in.

Second, it has often been argued that IBS is really a collection of disorders that all have a different underlying pathophysiology (or simply different short-term symptom triggers). Using the above protocol it may be possible to empirically disentangle such sub-disorders from the broader IBS (exemplified in figure 41).



Figure 41: Subgroup identification analyses using predicted treatment responses can break down IBS into more specific disorders.

Although subgroup identification analyses have been attempted in IBS on the basis of several variable types[1,8], a link with treatment outcome is usually missing. One can use predicted treatment responses to form patient subgroups, and subsequently characterise these for biomarker profiles and/or results of clinical tests.

Concluding remarks

IBS research undergoes continuous development. It has evolved from the previous-century paradigm of "IBS is merely a psychological disorder" to a biopsychosocial model. The functional-organic dichotomy has proven to be one of blurred lines, as the molecular basis of IBS physiology is slowly being unravelled. We and others have shaped a research framework for personalised IBS management in the next few decades, which intends to integrate symptom patterns ('the what') and mechanisms ('the how'). Hopefully, personalisation of IBS management leads to symptom improvement for a substantial proportion of patients, even though no treatment will ever be a holy grail. Research is thus rapidly generating knowledge and moving the frontiers of the field of IBS.

It is, however, equally important that the science finds its way into society. On this aspect there is a need for improvement. The internet and other mass media are currently dominated by pseudo-scientific information, leading to confusion about IBS in society. Amongst physicians there is lagging uptake of state-of-the-art knowledge and management practices, and IBS is still widely considered a diagnosis of exclusion. Finally, IBS remains a social taboo, thereby maintaining the social isolation that many patients experience. The irony is that academia, too, has an isolated position until it seeks active interaction with other stakeholders in the field. Let this be the goal of research: with good collaborative efforts by researchers, patient societies, physicians, industry, and mass media, for IBS to become an open and discussable topic in society.

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PERSONAL NOTES

Acknowledgements

Dear reader,

I would like to use these pages to express gratitude to those who have made the past years into a positive experience, despite the high demands associated with this PhD.

I wish to thank all the colleagues in Sweden for making 2017 into the nicest year I have had. Cecilia, your positive energy is contagious, and seeing you and your family shine after your own PhD defence was one of the happiest moments. I would love to return the hospitability someday if you ever happen to visit the Netherlands. Irina, thanks for all the times we have *fikat*, for all the chats, and for your always positive presence. You are up next! Thanks to Johanna, Sean, Navkiran, Imran, Annikka, and Axel for our shared stays at conferences in Chicago, Cork, and/or Barcelona. I would also like to genuinely thank all the other PhDs and students (Alex, Bani, Dağsu, Elisabet, Ellinor, Esther, Ida, Jenny, Jessica, Jonas, Joost, Karoline, Katarina, Luiza, Marcus, Milly, Pia, Sanna, Sara, Sofia, Stina, and Åsa), and the nurses and other colleagues (Angeli, Björn, Cecilia, Gisela, Gunilla, Karin, Lena, Maria, Nima, Paula, Pernilla, Sofie, Stine, and Valeria)! I will carry a bit of Sweden with me wherever I go.

Special thanks to Daniëlle and Dongxing for 'speaking the same language' as fellow foreigners in the office in Belgium. Our common time felt way too short; hopefully we will all stay in touch! Thanks to team Alma (Anneleen, Kathrin, Louis, Qiaoling, Sander, Shu) for all the funny chats and attempts to figure out what type of food it actually was we were having. Further thanks to the colleagues of LabGas (Boushra, Doreen, Eddy, Giao, Imke, Jessica, Julie, Lise, Nathalie, Taiana, Valerie) and the 'stellar team' (Anne-Christin, Annelies, Ans, Brecht, Chamara, Charlotte, Florencia, Hannelore, Hideki, Jasper, Jolien, Joran, Karen, Lucas, Nick, Pieter, Wout) for the memorable lab retreats. For you:

The heroes of the stellar team
Morally pure, but also keen
A Jacuzzi, some wine
The next morning at nine
The stars had dyed the water green

Thanks to my dear family for putting up with me in the final months. I will not have been the best company, and over the years you have been exposed to my progressively cynical view of science. Apologies for this, and I expect to soon regain the time and energy for the basic things in life.

Finally, Lukas, Magnus, Jan, and Hans, I greatly appreciate the freedom you have allowed me in my work. Seeing our department makes me realise how valuable and rare this is. This may be my final chapter in science. Hoping you understand:

Science
Idealistic
For health
With analytic
Critical thinking
Curiosity, tickling
Free with heuristics
Meticulous in statistics
Time turns you a sceptic:
FODMAPs and prebiotics?
Not particularly distinctive!
Analyses done, but still erratic
The article's at best poetic, but
Please, Gods…, 'tis for silver rapids
A far clock ticked as time went by.

Greetings, Respected Dr E. Egbert, on behalf of all co-authors:

Dylan;

Edgar;

Ernest;

Äggbert;

Jianyao;

Försvunnen doktorand.

…nu försvinner jag

Personal contributions

This thesis was fully written by Egbert Clevers, with feedback given by all co-authors (journal papers) and specifically Lukas Van Oudenhove and Magnus Simrén (other chapters).
The personal contributions of Egbert Clevers to the 5 journal papers were as follows:

	Rome IV factor analysis	Comorbidities of IBS	Psychological features of IBS	Food and stress as triggers	Food-stress-symptom diaries
Study design	-	-	-	-	x
Funding	-	-	-	n/a	n/a
Ethics procedures	-	-	-	-	x
Study logistics	-	-	-	-	x
Data collection	-	-	-	-	x
Analysis initiative	-	x	-	x	x
Analysis design	x	x	x	x	x
Data analysis	x	x	x	x	x
Manuscript	x	x	x	x	x
Revision	x	x	x	x	x

Conflicts of Interest

Egbert Clevers has no conflicts of interest.

About the author

Egbert Clevers was born on April 16th 1990 in Venlo, the Netherlands. Egbert followed bilingual education at secondary school 'Den Hulster' in Venlo until 2008, and then went to Maastricht University to do a BSc Biomedical Sciences and MSc Molecular Life Sciences.
In 2013 he combined a job as epidemiologist at the '*Dienst Gezondheid & Jeugd*' in Dordrecht, the Netherlands, with the MSc Health Food Innovation Management in Venlo. The thesis was done at McMaster University, Hamilton, Canada.
In 2015 Egbert started a double PhD at KU Leuven, Belgium, and the University of Gothenburg, Sweden, spending roughly 2 years at both sites.

His academic career has synthesised the following journal articles:

- Clevers E, Nordqvist A, Törnblom H, Tack J, Masclee A, Keszthelyi D, Van Oudenhove L, Simrén M. Food-symptom diaries can generate personalised lifestyle advice for managing gastrointestinal symptoms. Submitted.
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