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Symptom patterns in irritable bowel syndrome | Egbert Clevers

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SYMPTOM PATTERNS IN IRRITABLE BOWEL SYNDROME

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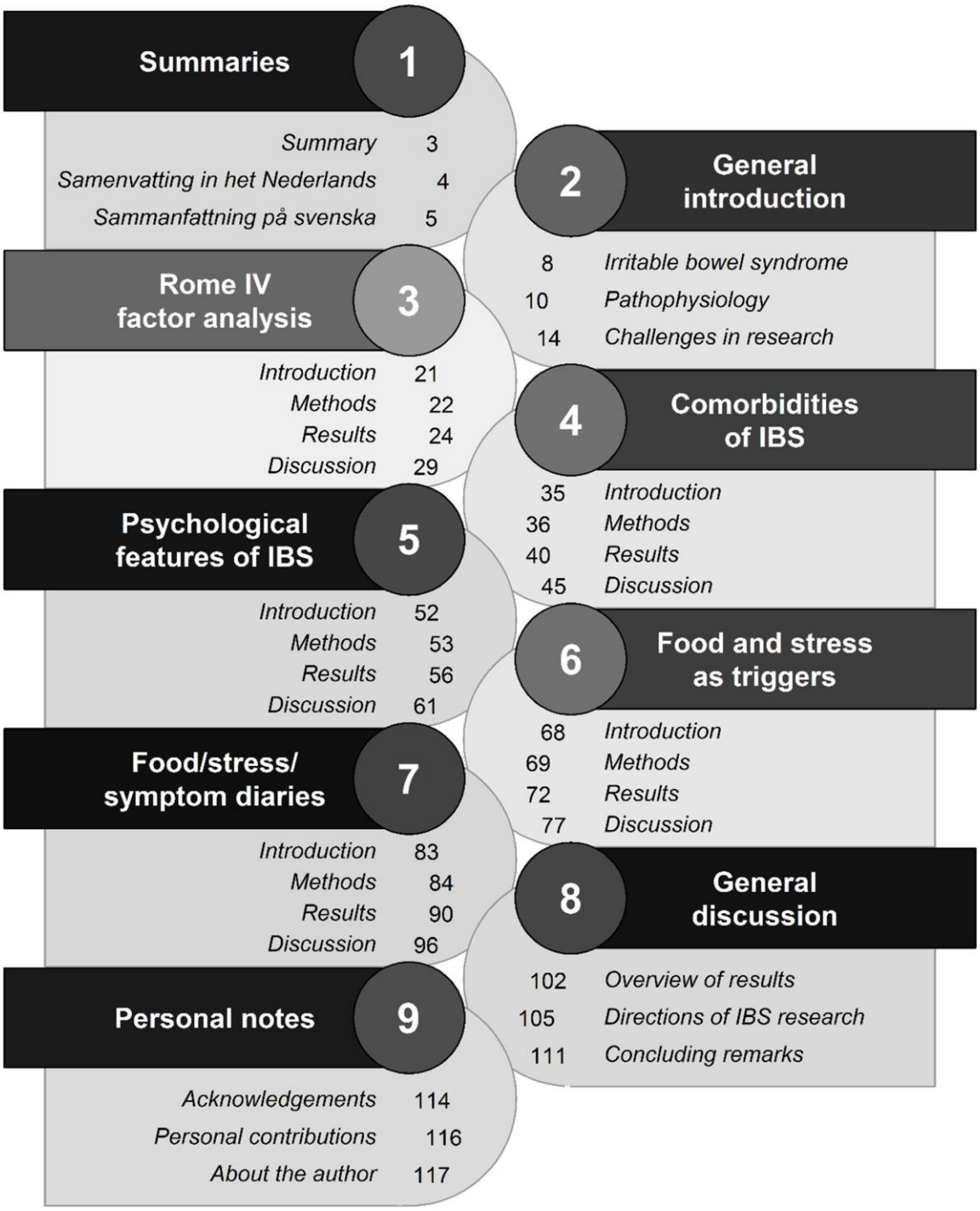
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Summary

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).

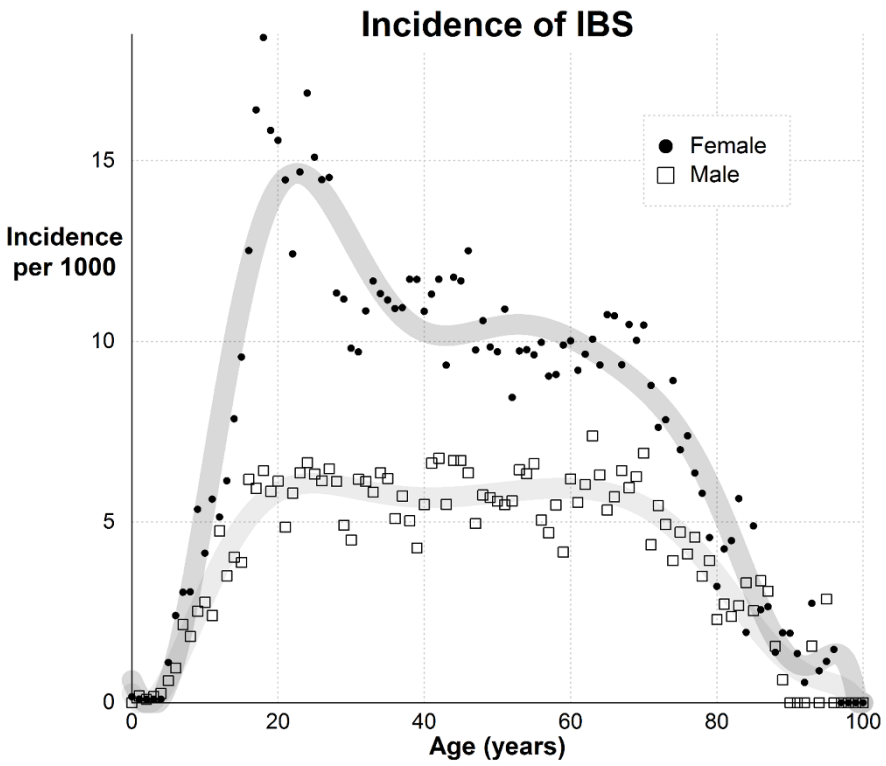

Figure 2: Incidence of irritable bowel syndrome (IBS) diagnoses in Flanders, Belgium. Data source: study 2.

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].

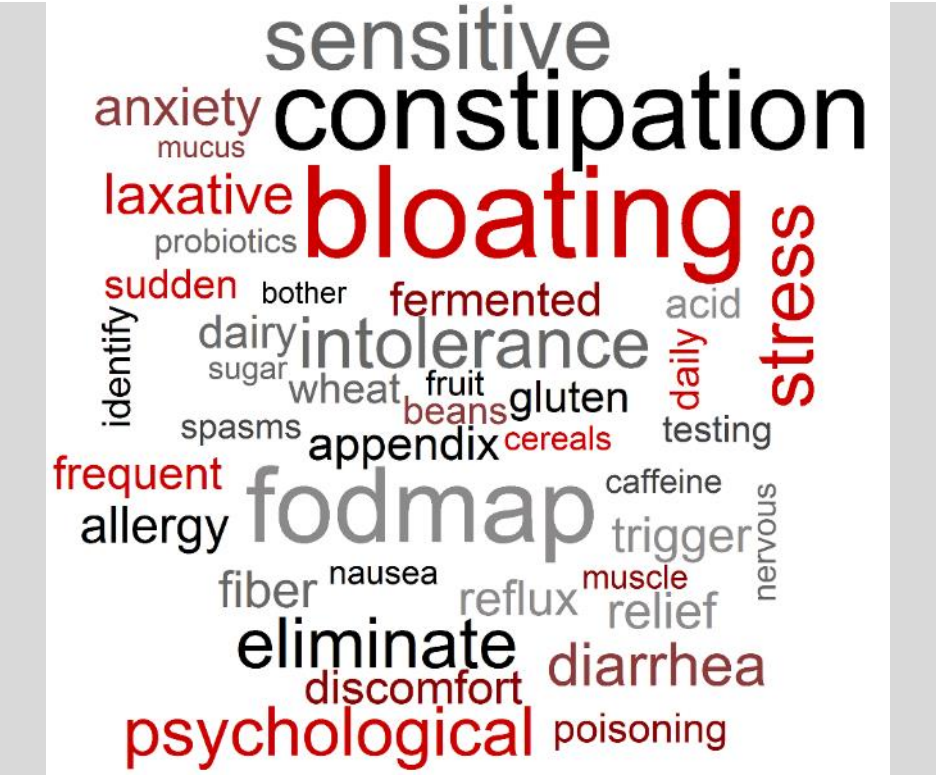

Figure 3: Word-cloud extracted from 91 IBS fora, adjusted for that of inflammatory bowel disease.

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.

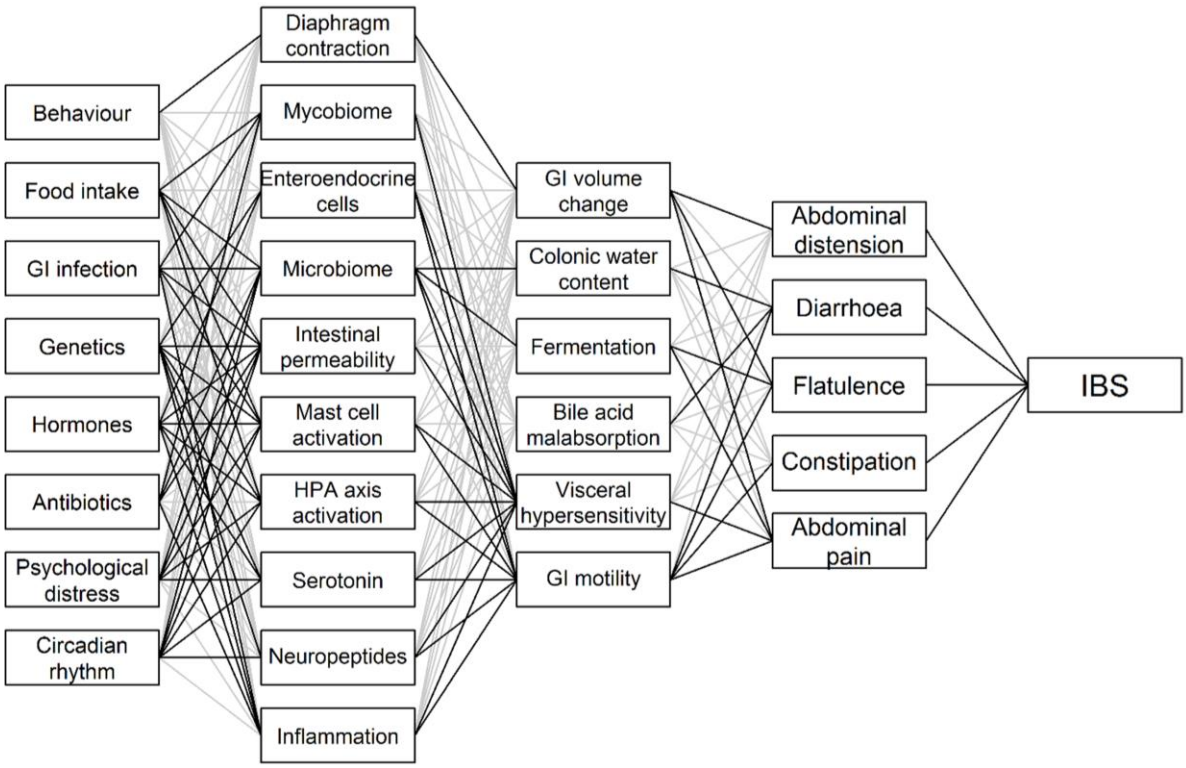

Figure 4: Pathophysiology of IBS, shown as a neural network. Darker lines represent some of the better characterised mechanisms.

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).

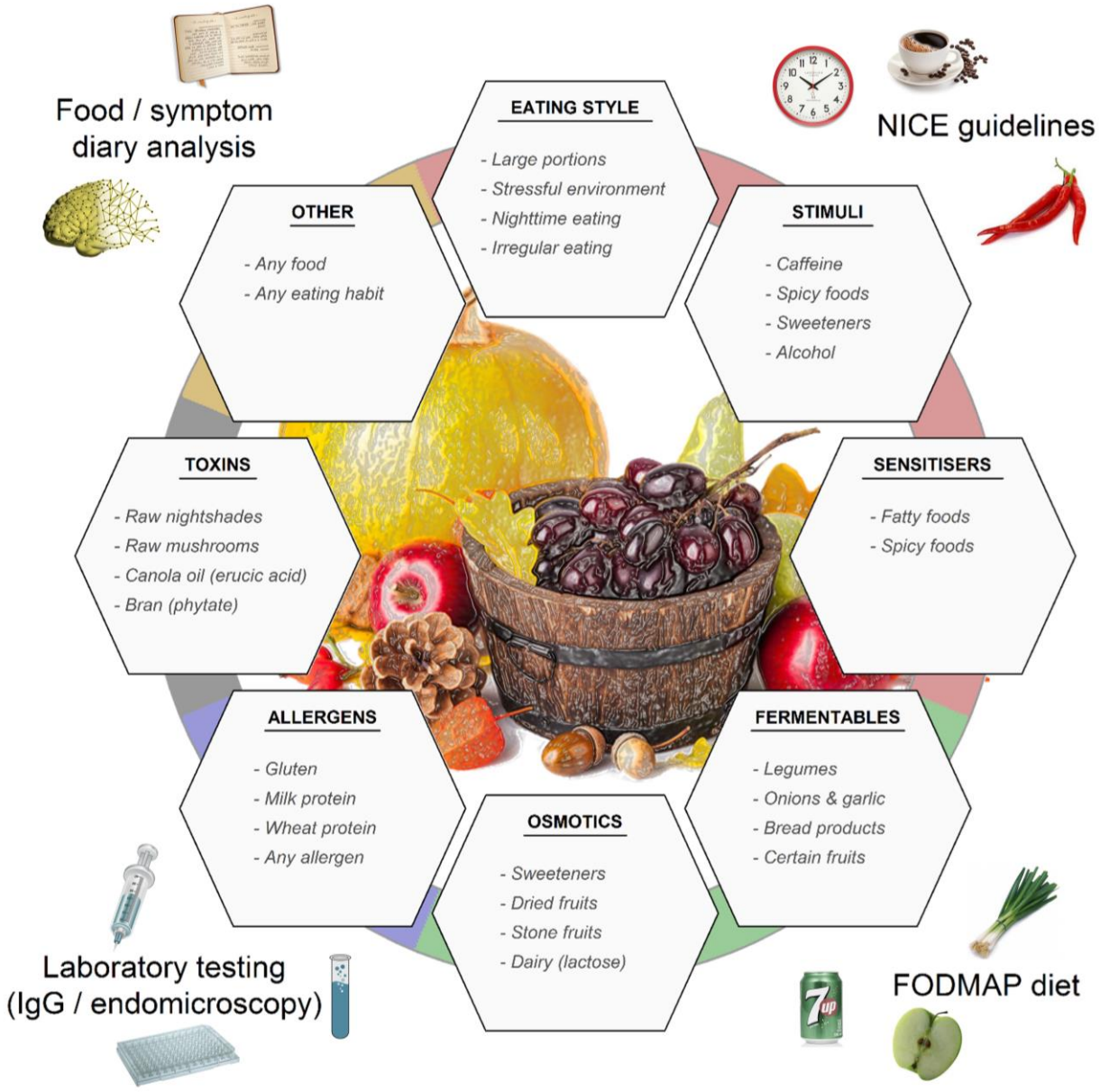

Figure 5: Mechanisms by which the diet can trigger GI symptoms, and some diet strategies that can be used to address these.

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].

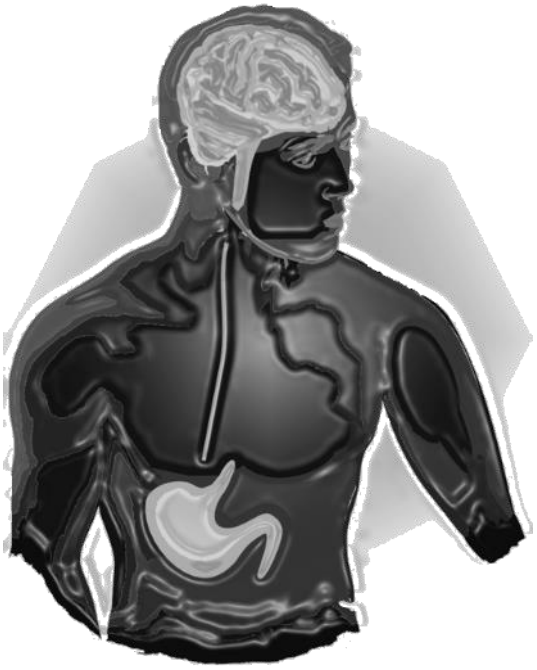

Figure 6: The brain and GI tract communicate.

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.

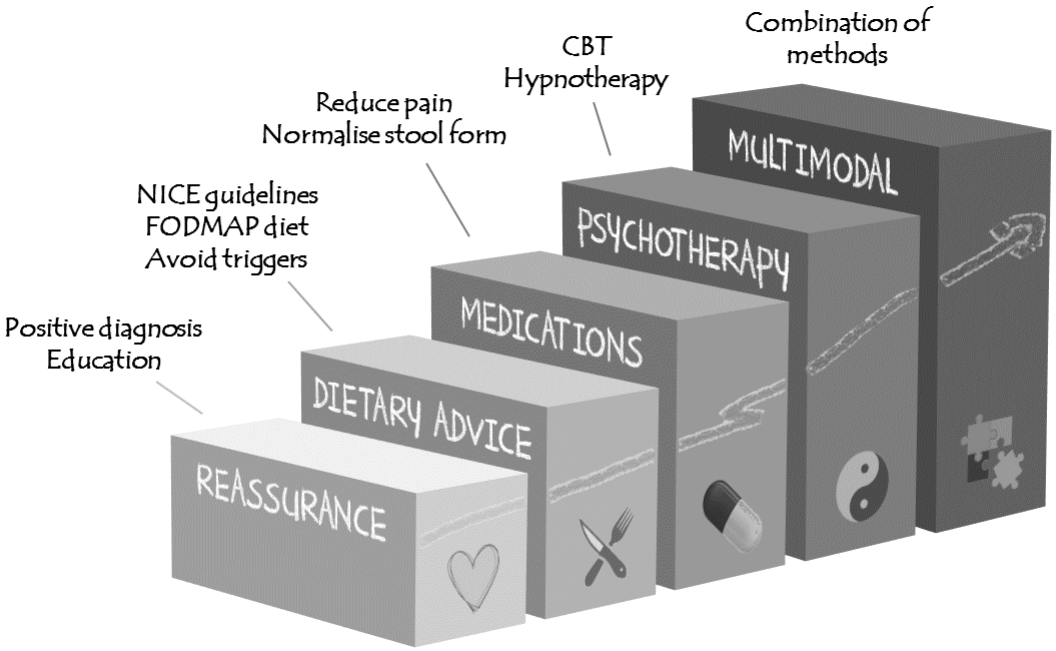

Figure 7: Current clinical management of IBS is a stepwise approach based on symptom severity.

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].

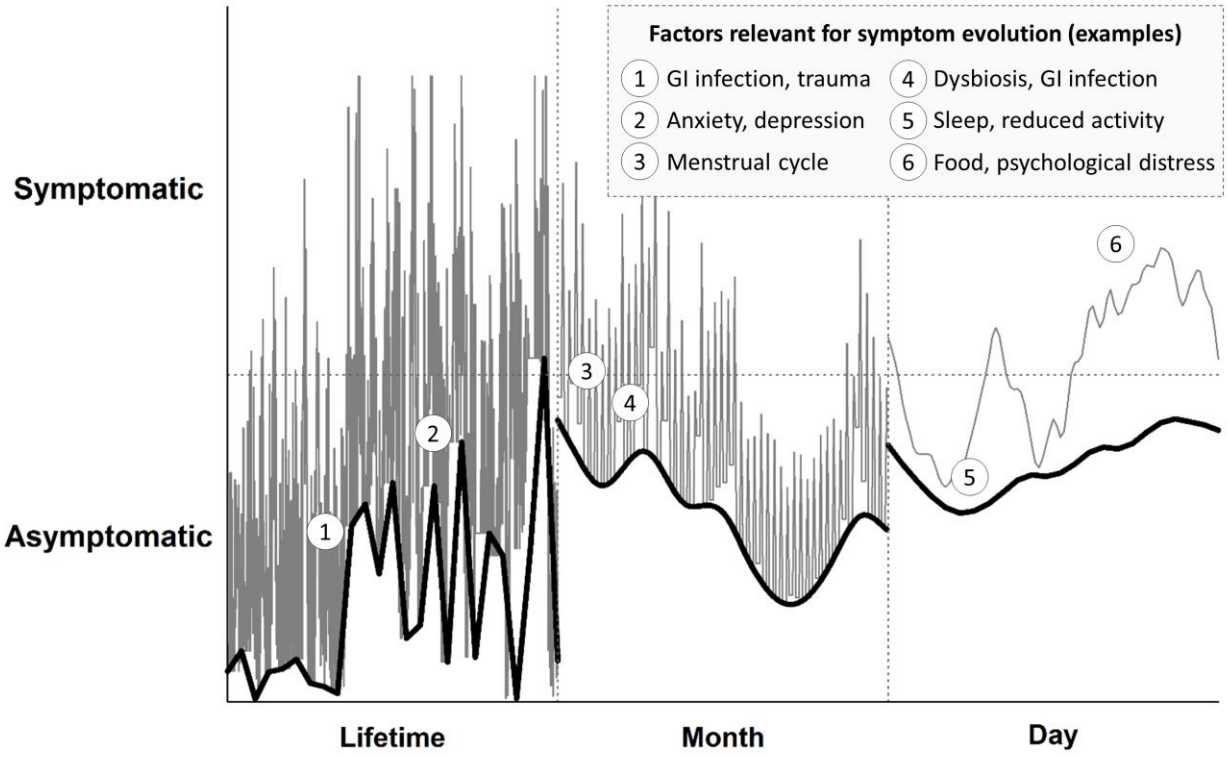

Figure 8: Proposed evolution of GI symptoms and factors influencing this. The thick black line represents a latent state of the GI tract.

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.

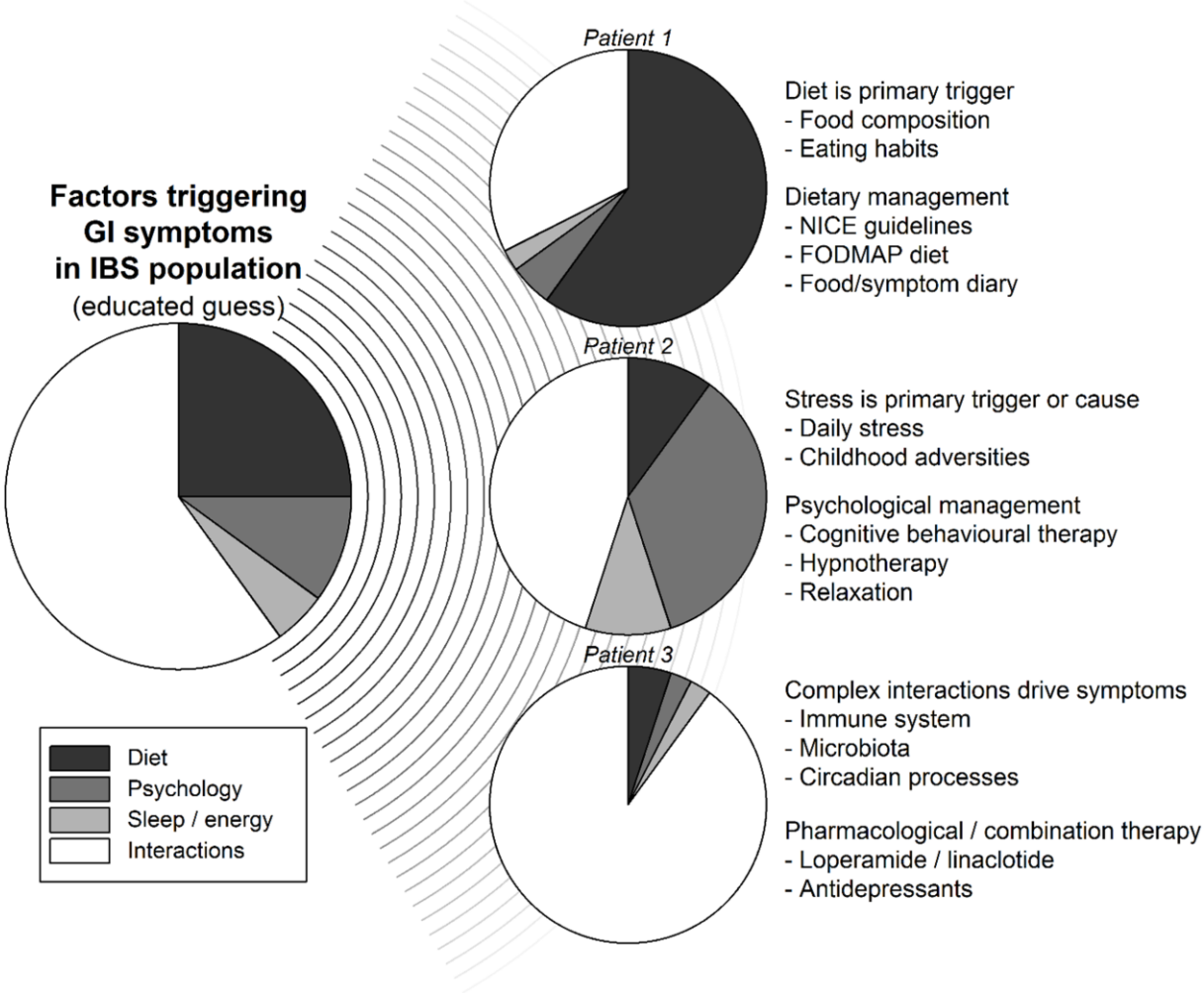

Figure 9: Several factors can cause or trigger GI symptoms (left). However, this will differ from patient to patient (right). Percentages in the pie charts are a guesstimate based on treatment responses to dietary or psychological interventions, as well as within-person correlations between dietary and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

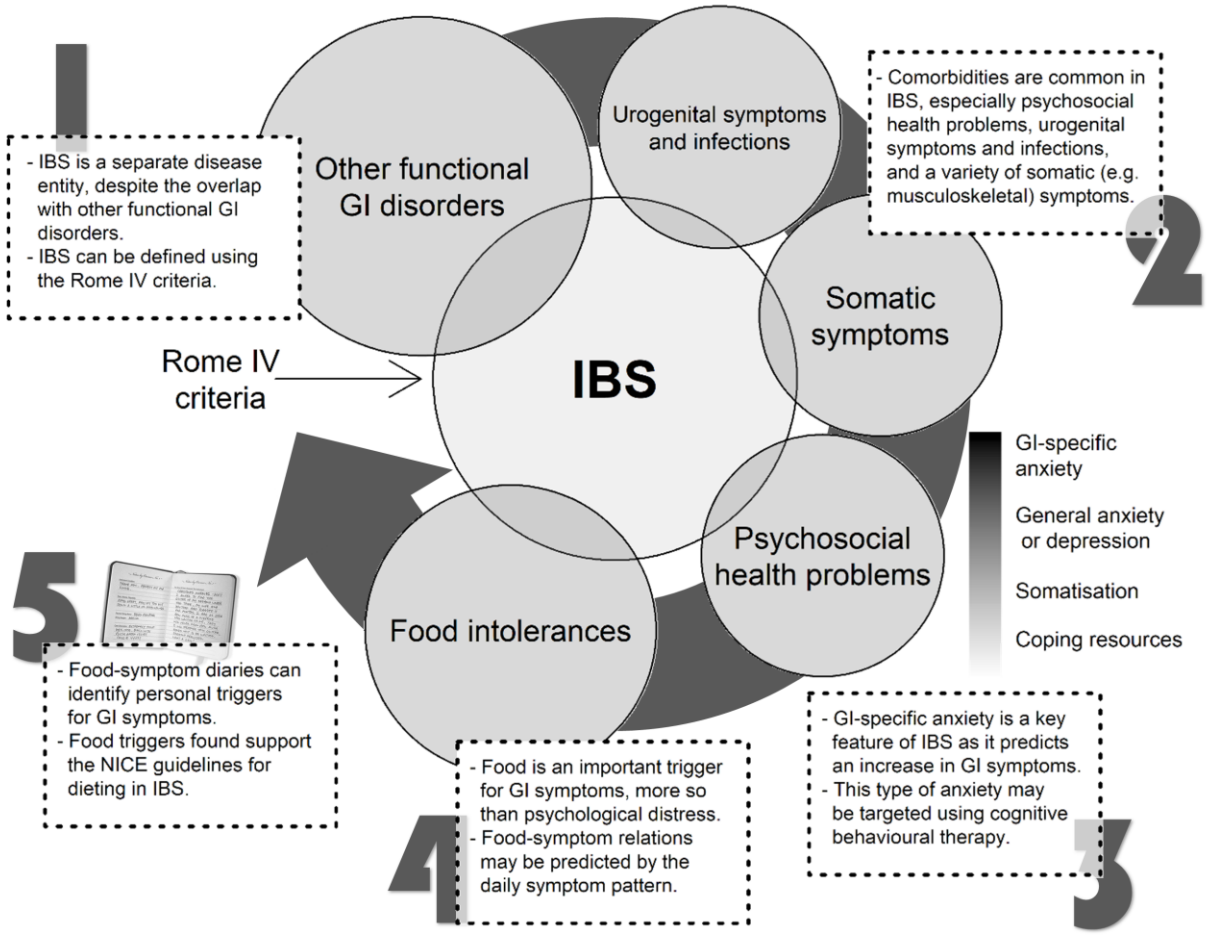

Figure 33: Simple overview of conclusions drawn from the 5 studies in this thesis.

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.

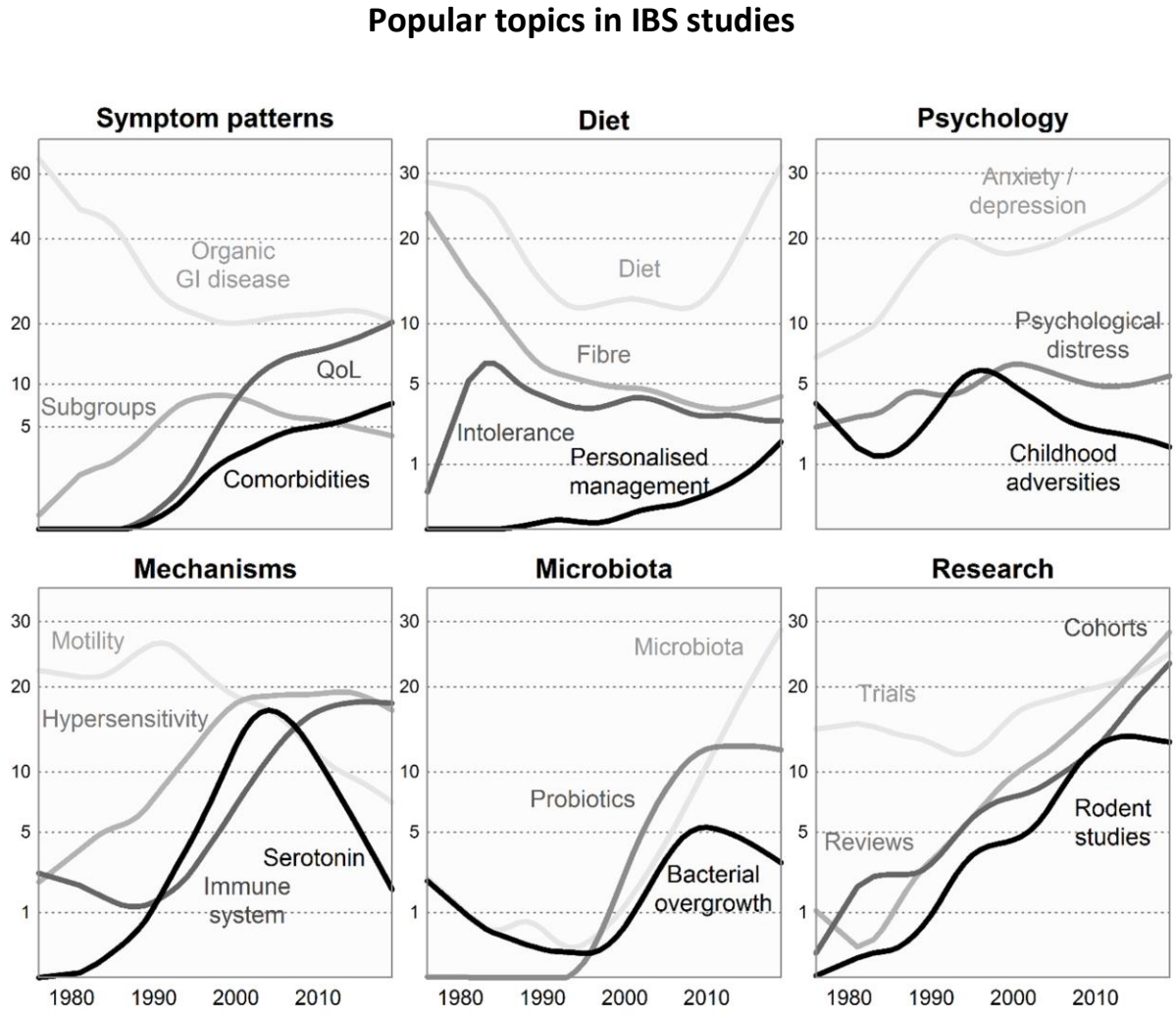

Figure 34: Of 9640 IBS study abstracts, trends in mentions of specific topics. Y-values are %s of articles a year on a square root scale.

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).

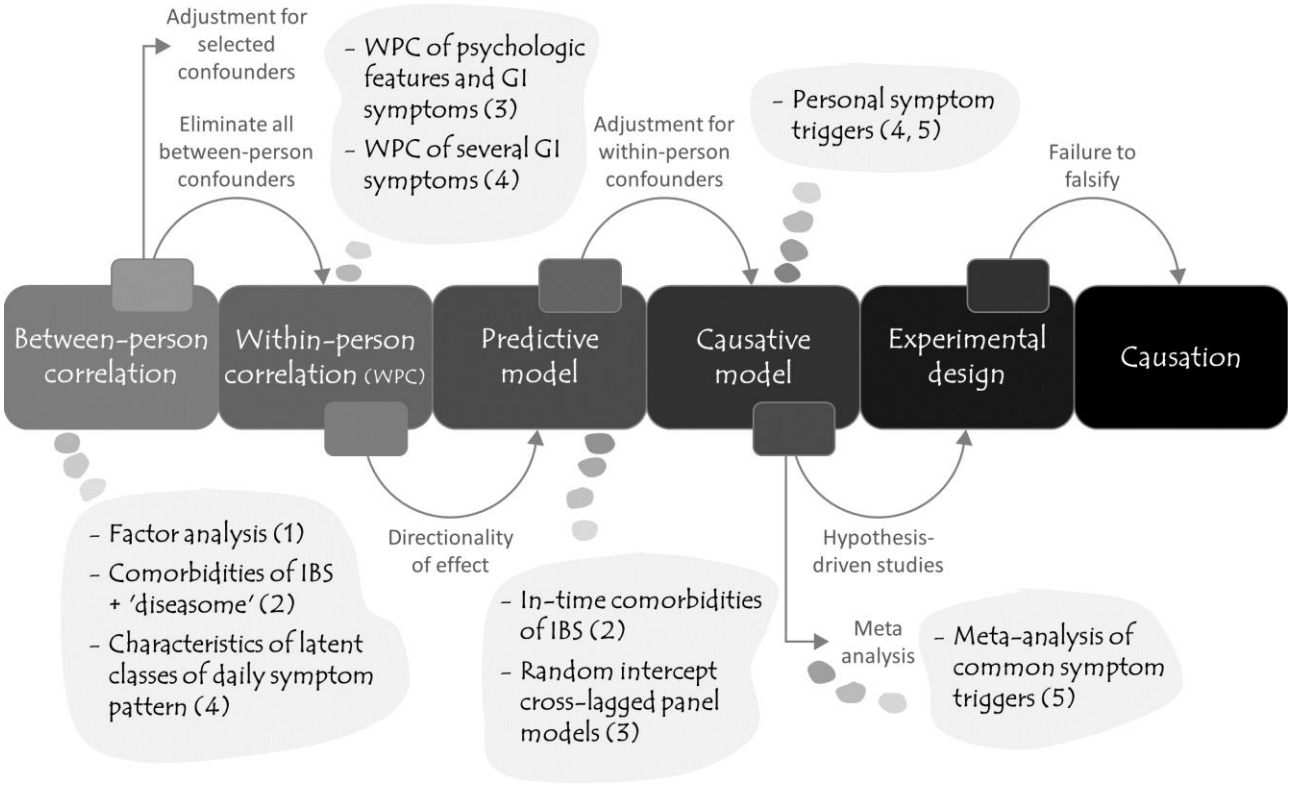

Figure 35: Causality inference in the 5 studies covered in this thesis.

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.

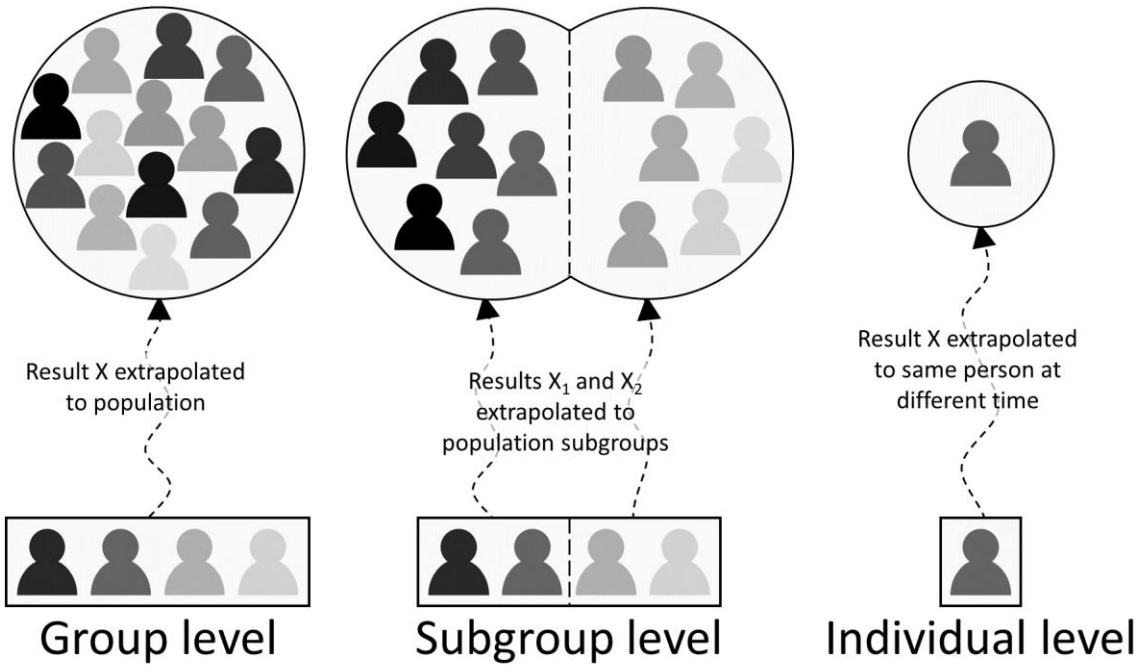

Figure 36: Research on the group level, subgroup level, and individual level (rectangles) lead to different generalisations (circles).

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.

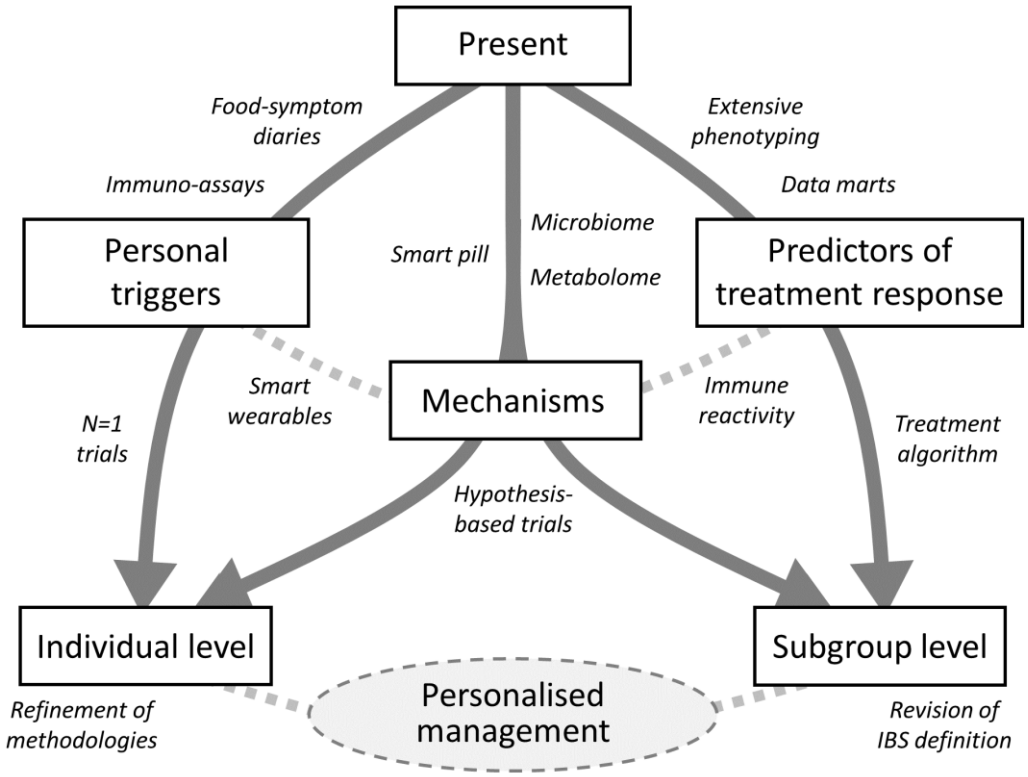

Figure 37: Proposed research framework for personalised management of IBS.

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.

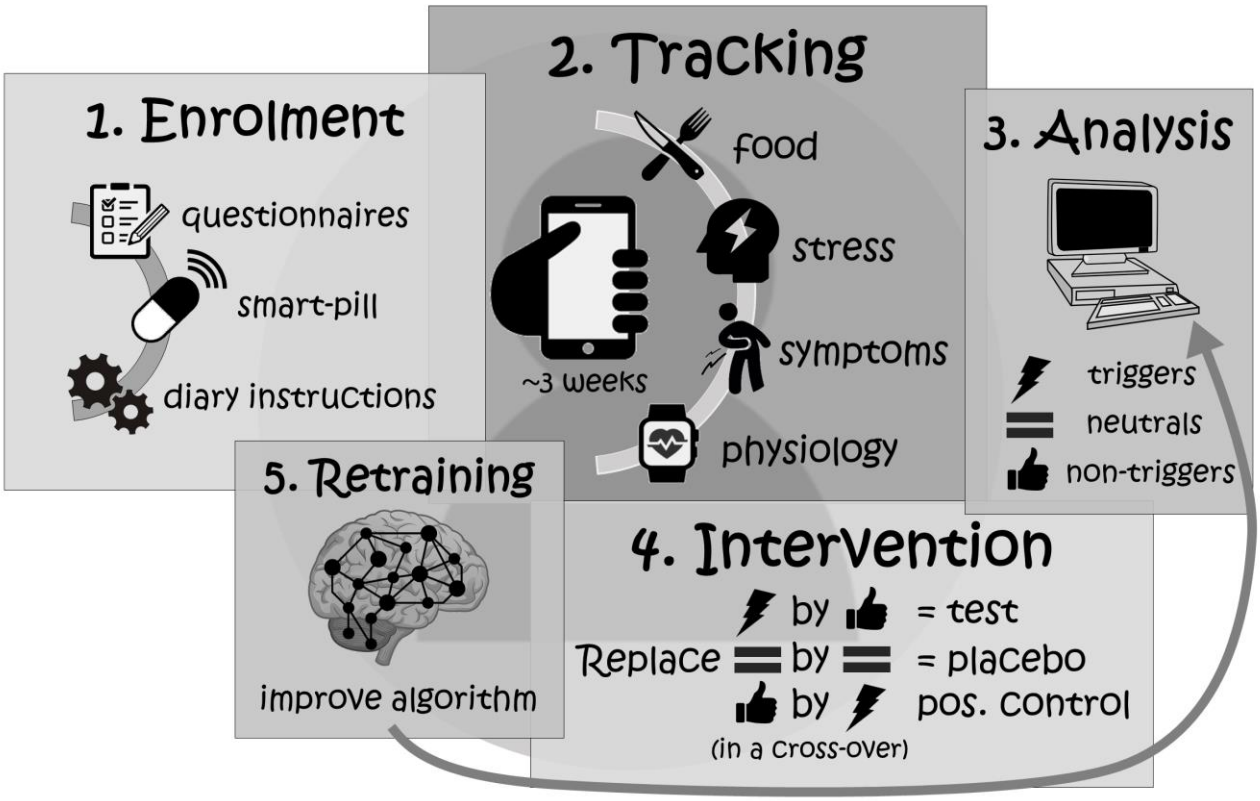

Figure 38: Suggested protocol for identifying personal triggers for GI symptoms in IBS.

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.

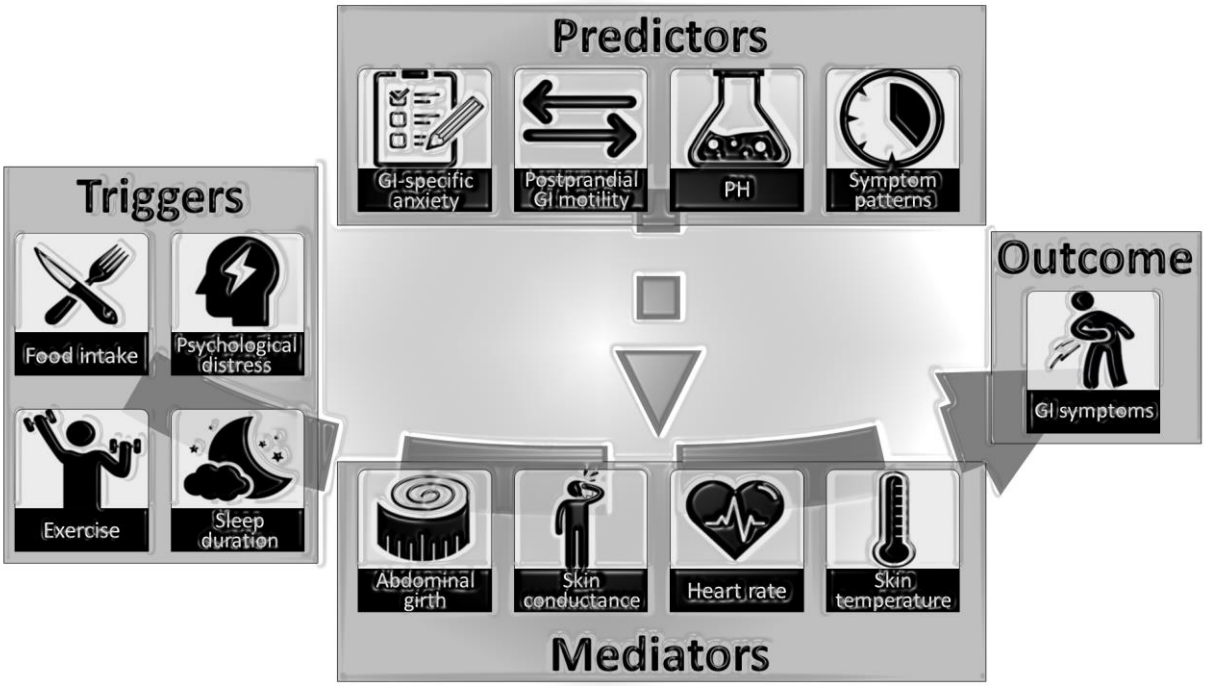

Figure 39: Big data tracking studies in IBS have many functionalities.

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.

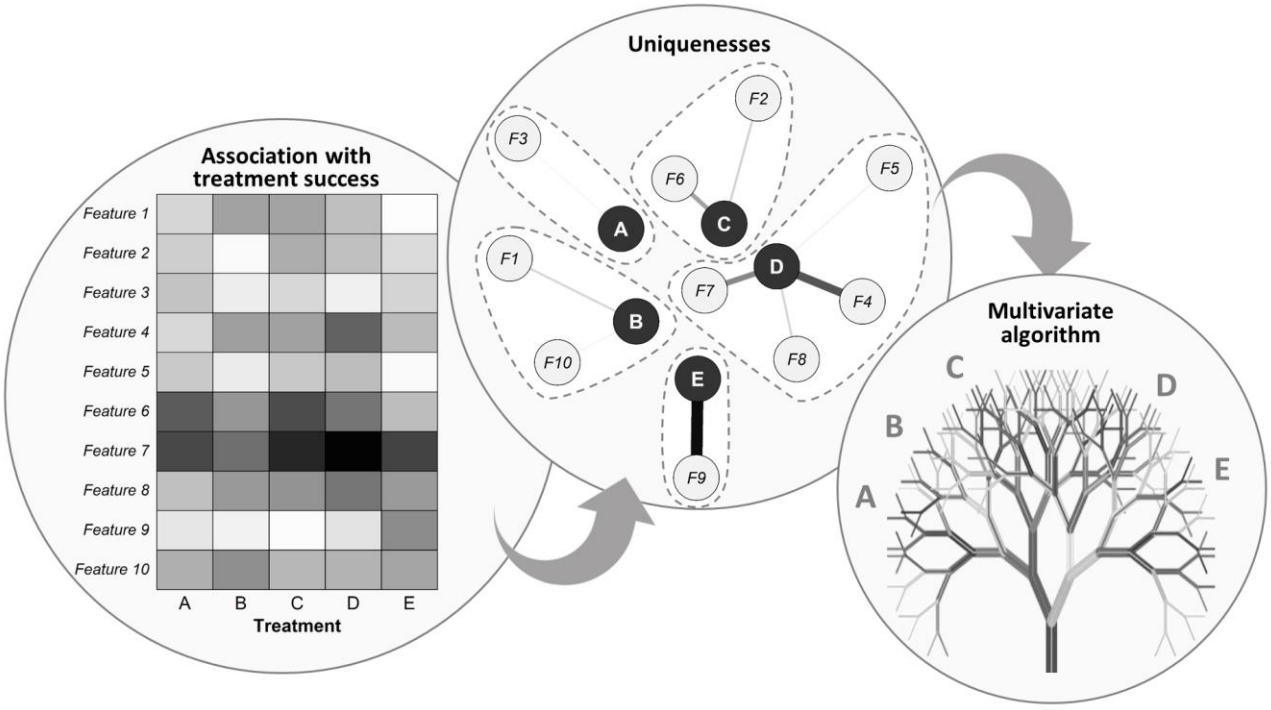

Figure 40: Treatment algorithm applications range from simplistic bivariate designs to complex multivariate trees.

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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