Subjective food hypersensitivity:

Lifestyle and psychological factors

Ragna Lind

Thesis for the degree philosphiae doctor (PhD) at the

University of Bergen, Norway

2010

Faculty of Medicine, Institute of Medicine,
Section for Gastroenterology, University of Bergen, Norway

Department of Medicine, Section for Gastroenterology,
Haukeland University Hospital, Bergen, Norway

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ACKNOWLEDGEMENT

The present work was carried out at the Department of Medicine, Section of Gastroenterology, Haukeland University Hospital, and at the Institute of Medicine, Section of Gastroenterology, University of Bergen, Norway. The thesis is based on work in the MAI-group at Haukeland University Hospital, which is collaboration between specialists in allergology, gastroenterology, nutrition and psychiatry, focusing on examination and treatment of adult patients with gastrointestinal symptoms self-attributed to food hypersensitivity.

I acknowledge the University of Bergen for financial support.

I am grateful to my supervisors for their help and support:
Arnold Berstad, for introducing me to science, for sharing his tremendous experience within clinical research, for his unique generous personality, patience and enthusiasm, and for always being available. I also appreciate his friendship and humour.
Gülen Arslan Lied, for friendship, support, and for sharing scientific knowledge.

My gratitude goes to Hege Randi Eriksen and her co-workers, for support, help, and stimulating discussions at Uni Health, University of Bergen.

I am grateful to several other persons for their contribution:
My co-workers in the MAI-group; Erik Florvaag, Agnete Hvidsten, Tone Tangen, Gudrun Kahrs, my fellow PhD students Vernesa Dizdar, Mette Morken, Kristine Lillestøl, Jørgen Valeur and Kine Gregersen for support, friendship, and for sharing scientific knowledge, and Snorri Olafsson and Ina Hjelland as co-authors in one of my papers.

Lars Birger Nesje and Solveig Hansen, the leaders of the Department of Medicine, Haukeland University Hospital, for working facilities.

Tormod Bjørkkjær and his co-workers at National Institute of Nutrition and Seafood Research (NIFES), and Anne Marita Milde and her co-workers at the Department of Biological and Medical Psychology, University of Bergen.

Kjersti H. Storemark, for friendship, support and always being available for logistic help, and Aud-Sissel Hjartholm and Gro Olderøy for laboratory advices and assistance.

My colleagues in the endoscopy unit, Department of Medicine, Haukeland University Hospital, for their support and discussions, and for always including me in work and private activities. A special thank to Berit Gausdal for always caring about me, encouraging me and believing that I one day should “be mounted on the wall” in the endoscopy unit.

Thank you to all the participants in this study, for cooperation and participation, which have made this study possible.

Thank you to my family, especially to my mother for always being available, both in happy and less happy days, and to my husband Ola and daughter Alice for encouragement and interest, and for being language advisers when I wrote this thesis.

Bergen, July 2010
Ragna Lind

ABBREVIATIONS

APC: *Antigen-presenting cells*

CATS: *The Cognitive Activation Theory of Stress*

CNS: *Central nervous system*

^{51}Cr-EDTA: *^{51}CR-labelled ethylenediaminetetraacetic acid*

CJSQ: *Cooper Job Stress Questionnaire*

CRF: *Corticotropin releasing factor*

DBPCFC: *Double-blind placebo-controlled food challenge*

EAACI: *European Academy of Allergology and Clinical Immunology*

ENS: *Enteric nerve system*

FODMAP: *Fermentable oligosaccharides, disaccharides, monosaccharides and polyols*

GI: *Gastrointestinal*

GSRS: *Gastrointestinal Symptom Rating Scale*

HADS: Hospital Anxiety and Depression Scale

IBD: *Inflammatory Bowel Disease*

IBS: *Irritable Bowel Syndrome*

IBS-SQ: *Irritable Bowel Syndrome Symptom Questionnaire*

INF-γ: *Interferron-gamma*

LCPUFA: *Long chain poly unsaturated fatty acid*

LTB_4: *4-series leucotienes*

MHW: *Modern Health Worries*

PUFA: *Poly unsaturated fatty acid*

QoL: *Quality of Life*

SF-Nepean: *Short form of the Nepean Dyspepsia Index*

SHC: *Subjective Health Complaints*

SHC-GP: *Subjective Health Complaints Inventory minus 14 questions (pseudoneurology and gastrointestinal complaints)*

TGF-β: *Transforming growth factor- beta*

Th_0-cells: *Naive T-cells*

Th_1-cells: *T helper 1 cells secrete cytokines like IL-2, IFN-γ, and TNF- α. The Th_1-cells are responsible for activation of cytotoxic T lymphocytes and a delayed-type of hypersensitivity.*

Th_2-cells: *T helper 2 cells secrete cytokines like IL-4, IL-5, IL-6, IL-10 and IL-13. This subset*

function more effectively as a helper for B-cell activation and production of antibodies.

T_c-cells: *T cytotoxic cells have lytic cabability, and recognise and eliminate altered self cells and genetically different cells in graft rejection reactions.*

Tregulatory cells, T_{reg} cells: *cells that have both CD4 and CD25 glucoproteins on their surface. They secrete TGF- β and suppress immune responses - they are instrumental in the maintenance of immunological tolerance.*

TNF-α: *Tumor Necrosis Factor-alpha*

UCL: *Utrecht Coping List*

UESS: *Ulcer Esophagitis Subjective Symptoms Scale*

VSI: *Visceral Sensitivity Index*

LIST OF PAPERS

The thesis is based on the following papers, referred to in the text by their roman numerals:

I Arslan G, Lind R, Olafsson S, Florvaag E, Berstad A. **Quality of Life in Patients with Subjective Food Hypersensitivity: Applicability of the 10-Item Short Form of the Nepean Dyspepsia Index.** *Digestive Diseases and Sciences 2004;49:680–687.* Reprinted with permission from Springer Netherlands.

II Lind R, Arslan G, Eriksen HR, Kahrs G, Haug TT, Florvaag E, Berstad A. **Subjective health complaints and modern health worries in patients with subjective food hypersensitivity.** *Digestive Diseases and Sciences 2005;50:1245-1251*. Reprinted with permission from Springer Netherlands.

III Lind R, Olafsson S, Hjelland I, Berstad A, Lied Arslan G. **Lifestyle of patients with self-reported food hypersensitivity differs little from controls.** *Gastroenterology Nursing 2008;31:401-410.* Reprinted with permission from Lippincott, Williams & Wilkins.

IV Lind R, Lillestøl K, Valeur J, Eriksen HR, Tangen T, Berstad A, and Arslan Lied G**. Job stress and coping strategies in patients with subjective food hypersensitivity.** *Scandinavian Journal of Psychology 2010;51:179-184.* Reprinted with permission from Blackwell Publishing.

V Lind R, Arslan Lied G, Lillestøl K, Valeur J, Berstad A. **Do psychological factors predict symptom severity in patients with subjective food hypersensitivity?** *Scandinavian Journal of Gastroenterology 2010; 45: 835-843.* Reprinted with permission from Taylor & Francis.

1. INTRODUCTION

1.1 BACKGROUND

Western societies have been facing a progressive increase of adverse reactions to food during the last ten years (1). As many as 20-30% of the general population report adverse reactions to food items, although only 1-3% of the patients have medically verified food allergy (2). Food hypersensitivity is defined as "objective reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" (3). The food items most frequently reported as cause of hypersensitivity reactions are cow's milk, wheat, fruits, hen's eggs, peanuts, fish, seafood, and food additives (4). In most of the patients the symptoms comply with those of the irritable bowel syndrome (IBS), with bloating, abdominal pain, irregular and incomplete defecation being the most prominent (5). In addition, symptoms from other organs such as fatigue and joint pain often co-exist (6).

It is commonly assumed that psychological and environmental factors typical of modern lifestyle such as stress and anxiety, modern nutrition, less physical activity, and reduced exposure to microbes are causally related to these non-allergic, hypersensitivity reactions to food (7-9).

While dermatological, respiratory, and systemic manifestations of food allergy are well known, reactions manifesting themselves in the gastrointestinal (GI) tract are less well characterised and understood (2). The symptoms are often variable and unspecific, and partly therefore difficult to diagnose and treat (2). This adds to the relatively limited armamentarium of diagnostic tools available for objective assessment of the afflicted individuals (2). When the symptoms remain unexplained following an extensive medical work-up, we have named the condition subjective food hypersensitivity (5).

1.2 HYPERSENSITIVITY REACTIONS

1.2.1 Immunological mechanisms

There are four types of hypersensitivity reactions, three occur within the humeral branch and are mediated by antibody or antigen-antibody reactions: IgE-mediated (Type I), antibody-mediated compliment activation (Type II), and immune complex-mediated (Type III). A fourth type depends of activated T-helper (Th) cells and T-cytotoxic ($T_{C)}$ cells within the cell-mediated branch (10), figure 1. Only type I and type IV reactions are supposed to be involved in food hypersensitivity (10).

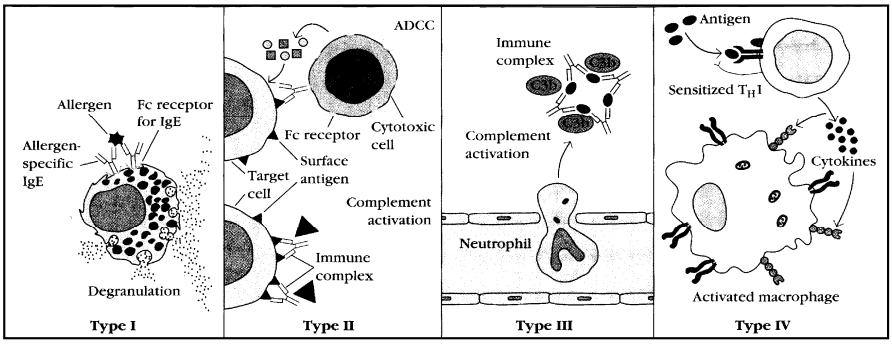

Figure 1. The differences in effectors molecules generated in the four types of hypersensitive reactions (10).

Type I reaction is an immediate, IgE-mediated reaction manifested within minutes or 2-4 hours after allergen exposure (10). During the sensitisation phase antigen presenting cells (APC), including B-cells and dendritic cells present the allergen peptide to T-helper 2 cells (Th_2-cells), resulting in a bias toward a Th_2 form of immune response with production of IL-4, IL-5, and IL-13 cytokines. The activated Th_2 cells induce B-lymphocytes to produce memory cells and plasma cells, the latter producing IgE antibodies. The IgE class of antibody binds with high affinity to Fc receptors (FcεRI) on the surface of tissue mast cells and blood basophils. A later exposure to the allergen cross-links the membrane-bound IgE causing activation of mast cells and basophiles with release of histamine, leukotriens, and other mediators including tumor necrosis factor-alpha (TNF-α) and secondary recruitment and activation of eosinophils and neutrophils (11). By releasing such mediators, mast cells are believed to regulate epithelial ion transport, vascular permeability, smooth

muscle contraction and peristalsis, fibrogenesis, and enteric nerve function. Moreover, mast cells contribute to the recruitment of inflammatory cells such as neutrophils and eosinophils and to oedema formation, typical feature of allergic inflammation (Figure 2). The clinical manifestations of type I reactions can range from acute life-threatening conditions, such as shock with generalised urticaria, laryngeal edema, lower-airway obstruction, and hypotension, to delayed localised reactions, such as hay fever and eczema. The term allergy has come to be used interchangeably with Type I hypersensitivity (10).

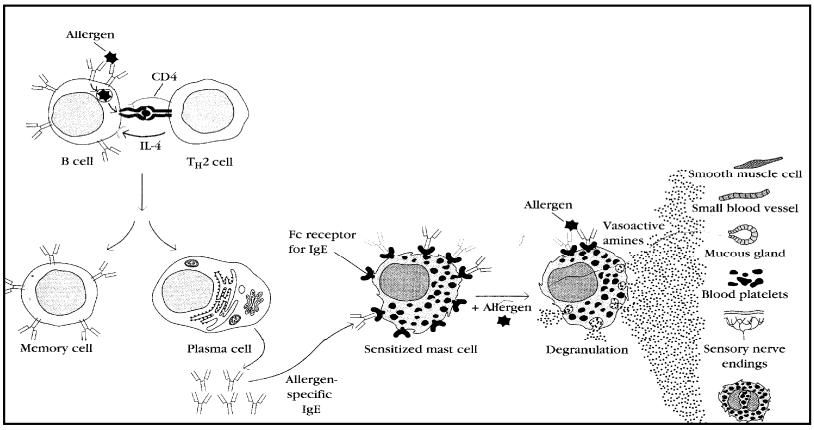

Figure 2. General mechanisms underlying an immediate type I hypersensitivity reaction (10)

Delayed- or type IV hypersensitivity reaction involves the cell-mediated branch of the immune system and is activated by IgG, IgA, IgM and IgD antibodies. Antigen activation of sensitised Th_1 cells induces release of various cytokines that cause macrophages to accumulate and become activated. The net effect of the macrophages is to release lytic enzymes that causing localised tissue damage (10). The presence of delayed patterns of food allergy is believed to be concealed in a variety of diagnoses such as migraine headaches, asthma, eczema, IBS, depression, chronic fatigue, fibromyalgia, panic disorder, and arthritis (12).

It has been estimated that humans consume approximately 100 tons of food during a lifetime (13). The GI barrier is a non-specific defence system consisting of gastric acid, digestive enzymes,

mucus, and an intact epithelial layer forming tight junctions and peristaltic movements (10; 14). Despite the barrier, about 2% of ingested food antigens are absorbed through the mature gut, and are transported throughout the body in intact form that may result in immunological responses (15). However, the most common consequence of this exposure is the state of hypo-responsiveness or tolerance (16). Mechanisms leading to mucosal tolerance include induction of cell death or cell anergy (11; 16). No specific IgE is produced, and eosinophils and mast cells remain in a resting state. This results in a state of controlled inflammation that characterises the normal gut mucosa and bowel function (17) (Figure 3), in contrast to a food hypersensitivity reaction.

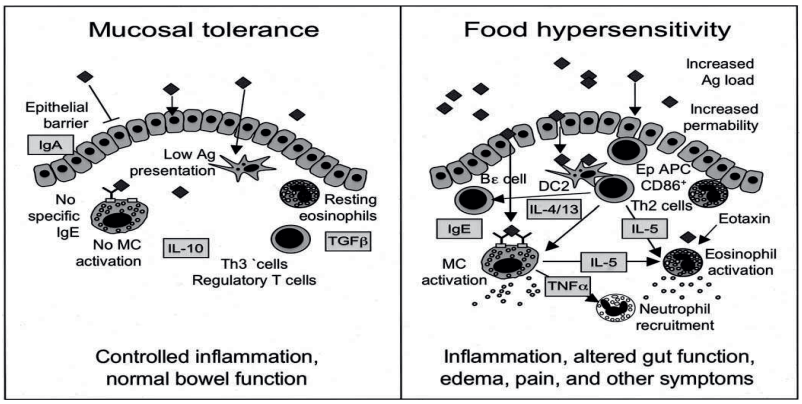

Figure 3. Mechanisms leading to mucosal tolerance or hypersensitivity to food antigens in the GI tract (17).

1.2.2 Hygiene hypothesis

Atopy depends on a genetic predisposition for the development of immediate hypersensitivity reactions against common environmental antigens (atopic allergy), most commonly manifested as allergic rhinitis but also as bronchial asthma, atopic dermatitis, and food allergy (11).

The “hygiene hypothesis” from 1989 reported an inverse relationship between family size and birth order and development of atopic disorders, and proposed that a lower incident of infection in early childhood or acquired prenatally could be cause of the rise in allergic disease (18). Subsequently, the concept was further evolved into a broader notion that declining microbial exposure is a major causative factor in the increasing incidence of atopy in recent years (18). Epidemiological, clinical

and animal studies suggest that broad exposure to a wealth of commensally, non-pathogenic microorganisms early in life are associated with protection, not only against IgE-mediated allergies, but possibly also against type-1 diabetes and inflammatory bowel disease (IBD) (18-20).
One pathways for protective effect of microbial exposure against atopy may involve the bacterial flora of the gut (21; 22). Several authors have found that non-allergic children had a greater prevalence of *Lactobacilli* and *Bifidobacteria* in their gut compared with the flora of allergic children, indicating these lactic acid bacteria may help prime or maintain normal gut flora and preserve intestinal mucosal integrity (21; 22). As a consequence, effects of antibiotics, domestic cleaning and hygiene on the bacterial colonisation of the gut in early years of development, and subsequent allergy development are extensively debated (23-25).

1.2.3 Food hypersensitivity

Until the late 1990`s the classification of adverse reactions to food was divided into toxic and non-toxic reactions, the first may be due to naturally occurring in food ingredients (e.g. histamine fish poisoning or alfatoxins in peanuts) or be added during food preparation (3). Non-toxic reactions were classified into food allergy (immune mediated) or food intolerance (non- immune mediated) reactions. However, in clinical practice it is often unclear whether the problem is allergy or intolerance due to the time between ingestion and symptoms, and insufficient diagnostic tools (3).

In 2001 European Academy of Allergology and Clinical Immunology (EAACI) revised the classification, and the term food hypersensitivity is now covering all kinds of adverse reactions to foods (3). The nomenclature was updated in 2003 (26). The term food allergy should be used when immunological mechanisms have been demonstrated, which includes both IgE-mediated and non-IgE mediated reactions. All other reactions, which have sometimes been referred to as food intolerance, should be termed non-allergic food hypersensitivity (26) (Figure 4). The main difference between food allergy and non-allergy food hypersensitivity is that food allergy is caused by a protein interacting with the immune system, and food hypersensitivity is caused by substances in foods other than proteins, with no involvement of the immune system (26).

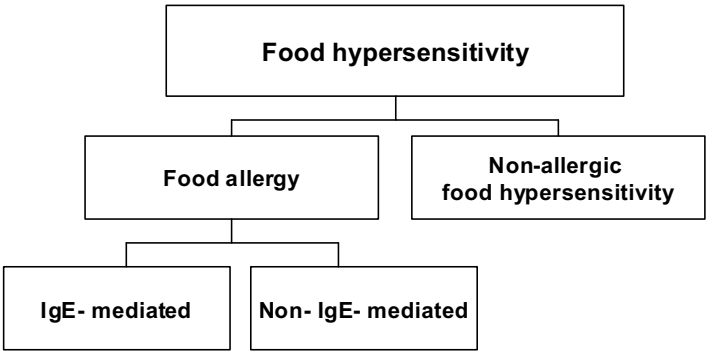

Figure 4. Nomenclature of food hypersensitivity (26)

Allergic reactions are of considerable concern because of a rapidly increasing prevalence during the past few decades (27). The prevalence of food hypersensitivity is greatest in the first few years of life (27). Previous studies conducted in England and The Netherlands, France and Denmark show that 15% to 45 % of the general population claim adverse reactions to food (4; 28-30). Approximately 25% of the United States` population believes that they have an allergic reaction to foods (4). The actual incidence confirmed by history and challenges suggests a prevalence rate closer to 2-8% in young infants and less than 2% in adults (4). Different types of food hypersensitivity (31) are presented in Table 1.

Table 1. Presentation of different types of food hypersensitivity (31).

	Gastrointestinal	**Cutaneous**	**Respiratory**
IgE- mediated food allergy	Oral allergy syndrome Gastrointestinal anaphylaxis	Urticaria Angioedema Red flushes	 Acute rhinoconjunctivitis Acute asthma
Mixed IgE and and cell-mediated	Allergic eosinophilic esophagitis Allergic eosinophilic gastroenteritis	 Atopic dermatitis	 Asthma
Non-IgE-mediated food allergy	Food protein-induced proctocolittis Food protein-induced enterocolittis	Contact dermatitis Dermatitis herpetiformis	Food-induced pulmonary hemosiderosis (Heiner`s syndrome)
Cell-mediated food hypersensitivity	Food protein-induced enterophaty Coeliac disease	Contact dermatitis Dermatitis herpetiformis	Food-induced pulmonary hemosiderosis (Heiner`s syndrome)
Non-allergic food hypersensitivity	Enzyme deficiency (lactose intolerance), infections (bacteria, virus and parasites), pharmacologic psychological factors (stress, anxiety, psychological disorders) and other factors (caffeine, alcohol and biogene amines)		

1.2.4 Food allergens

Although the diversity of the human diet is enormous, relatively few foods account for the majority of food allergies (4). In general, the most common food allergens in children worldwide are in milk and hen`s egg, but regional dietary habits and methods of food preparation clearly play a role in the prevalence of specific food allergies in various countries around the world (4; 32). For example, the consumption of peanuts in China and the United States is essentially the same, but there is virtually no peanut allergy in China (33). The Chinese eat predominantly boiled or fried peanuts, whereas the Americans eat almost exclusively dry-roasted peanuts, a process of which have been shown to increase the allergenicity of the peanut protein (34). Sesame allergy is frequent in Israel, probably because of early introduction to tahini, which is a sesame paste used in a variety of dishes (35). In Spain, the most frequent cause of food allergy is from a hidden allergen in Anisakis simplex larvae that infects fish or shellfish. This might be due to the habit of eating fresh raw anchovy marinated in vinegar (36). Another important dietary allergen is soy, the use which has spread in such a way that today it is almost impossible to make a diet without soy (36). The foods that most often cause allergy in adults are seafood and tree nuts as well as fruits and vegetables where the primary sensitisation mainly comes from pollen (36).

Unlike plant food or pollen allergens, almost all the animal food allergens have homologs in the human proteome that may affect the way in which they are recognised by the human immune system (37). Jenkins *et al.* (37) have shown that proteins with $\leq 54\%$ to human homology were all allergenic, whereas those with a sequence identity greater than 63% were rarely allergenic. The only exception is the cow`s milk allergen bovine serum albumin that is 76% identical to the human homolog. It is generally thought that this protein is a much less important cow`s milk allergen than, for example, the caseins (37). Newly, Commins *et al.* (38) suggested that IgE antibodies to carbohydrate epitopes can be an important factor in food allergy. They have shown that IgE antibodies to the carbohydrate galactose-α-1.3 (α-gal) is associated with an unusual form of delayed anaphylaxis, which follows after eating meat like beef, pork or lamb, that carries α-gal (38). These thoughts are different from established teaching on food allergy because this form develops in adult life, the reactions start 3 to 6 hours after eating the meat, and the patients generally have negative or weak responses to skin prick tests with meat extracts (38).

1.2.5 Diagnostic tests

No single test is able to identify all patients with food allergy or indicate the severity of the diseases (39). The most common tests are a detailed medical history**,** skin prick test, total – and specific IgE, atopy patch test, elimination diet and oral food challenge, which can be performed as open, single-blind or double-blind placebo-controlled food challenges (DBPCFC). For many years DBPCFC has been considered the "gold standard" for diagnosing food allergy (40). Some authors point out that the general lack of standardised methods for the oral challenges is a primary limitation of the DBPCFC (40). The procedure is also expensive, cumbersome and time-consuming. For research purposes, mediators that are released from mast cells and eosinophils (histamine, tryptase and eosinophil cationic protein) may be measured in serum, urine or stool (41-44).

A study by Santos *et al.* (45) showed that intraluminal administration of food antigens in patients with "true" food allergy induced a rapid increase in intestinal release of tryptase, histamine, and prostaglandin D. The increased release of these mediators was associated with a notable water influx (45; 46) (Figure 5). The symptoms are usually acute, short lasting abdominal cramps and diarrhoea (45). A major problem is that all traces of an allergic reaction might have disappeared at the time of investigation (45).

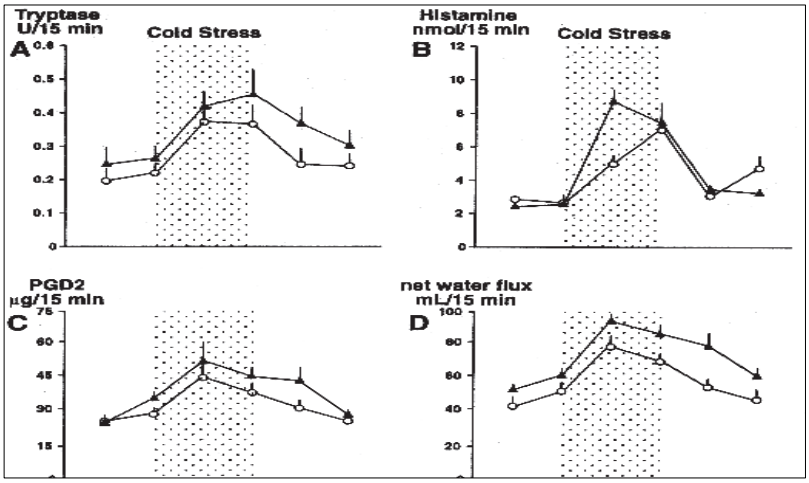

Figure 5. Effect of antigen challenge on jejunal release of (A) tryptase, (B) histamine, (C) prostaglandin D (PGD_2), and (D) water flux in healthy volunteers and patients with food allergy (46).

Other provocation tests are gastroscopic provocation tests to challenge the gastric mucosa with food allergens during upper endoscopy, or colonoscopic allergen provocation test where biopsies are taken from the provocation areas as well as from unprovoked caecal mucosa (42). Also, direct duodenal food provocation may be monitored by transabdominal ultrasonography, but further methodological validation is needed before its clinical utility can be determined (47).

1.2.6 Management and prevention

The cornerstone of food allergy management is to vigilantly avoid trigger foods and maintain readiness to treat allergic reactions, for example with self-injectable epinephrine (48). Currently, numerous strategies for definitive treatment are being studied, including sublingual/oral immunotherapy, injection of anti-IgE antibodies, cytokine/anticytocine therapies, Chinese herbal therapies, and novel immunotherapies utilizing engineered proteins and strategic immunomodulators (49). However, most of the clinical studies concerning these new therapies are still performed in animal models, but they do offer hope for better treatments in humans in the near future (48-50).

1.3 IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is one of the most common disorders encountered in modern medicine. It is a functional disorder of the lower GI tract whose clinical expression is characterised by abdominal pain and/or discomfort associated with bloating and disturbed bowel habits (51). The prevalence of IBS in western Europe and North America is estimated to be 5% - 25%, which accounts for about 20% - 50% of the referrals to gastroenterology clinics (52). In most studies, more females than males have IBS (52), and more than 60% of IBS patients report worsening of symptoms after meals (53).

The etiology of IBS is complex and still unclear (52). Proposed mechanisms include visceral hypersensitivity, altered GI motility and fermentation, post-infectious intestinal alterations, anxiety, depressions and diet (53; 54). The mechanisms behind the disturbances are thought to be a result of disturbed neural function along the brain-gut axis, a low-grade inflammation within the gut wall, and altered immunological function (55). Also, alterations in the gut flora, which can have an impact on the gut immune system and affect nerve function, has been a major focus of research in recent years (56-59) (Figure 6).

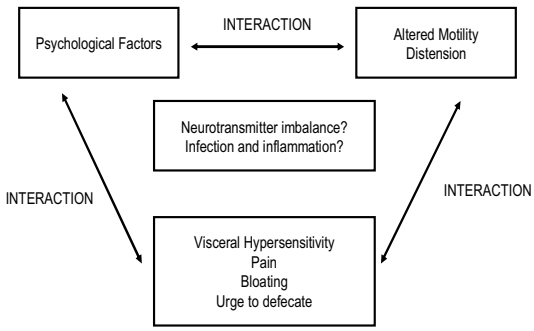

Figure 6. Suggested pathophysiology of the Irritable Bowel Syndrome (57).

In clinical research of IBS, most studies apply the definitions enshrined in the Rome II (60) or Rome III criteria (61), table 2.

Table 2. Diagnostic criteria in ROME III (61).

At least 3 days per month in the last 3 months with symptoms onset at least 6 months prior to diagnosis, associated with two or more of the following:

- Relief with defecation,
- Onset associated with change in frequency of stool
- Onset associated with change in form of stool

Symptoms that cumulatively lend support to the diagnosis of IBS:

- Abnormal stool frequency (>3 bowel movements per day and <3 bowel movements per week)
- Abnormal stool form (lumpy/hard or loose/watery)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abnormal distension

The process for developing these criteria started in 1989 in Rome with the Rome I Criteria for IBS established in 1992, the Rome II Criteria for IBS in1999, and to the recent Rome III Criteria in 2006. Rome II and Rome III incorporated paediatric criteria to the consensus (61). The changes from Rome II to Rome III reflect mainly updates in the literature and committee recommendations derived from these new data (61). In addition, a few modifications in the categories and criteria were made. Symptoms are now recommended to originate 6 months before diagnosis and be currently active for 3 months (61). Furthermore, there have been some changes in classification different categories of functional gastrointestinal disorders (61).

1.4 LIFESTYLE

Lifestyle can be understood in many different ways (62). In sociology, a lifestyle is the way a person or a group lives (62). This includes patterns of social relations, consumption, entertainment, and dress (62). Max Weber (63) distinguishes between two independent aspects of lifestyle; life conduct and life chances, and emphasizes lifestyle as means to social differentiation, which can be used to acquire or maintain a certain social status. Lifestyle is based not so much on what a person produces but on what she or he consumes (63). Lifestyle of an individual is understood as relatively stable patterns of behaviour and habits typical for the groups the individual belongs to, or the groups she or he wants to belong to (64).

Our lifestyle has changed markedly during the last two generations. Education patterns, gender roles and family structures, social patterns and habits, values and cultural status are very different compared with the lifestyle 30 years ago. The economy, especially in Western countries, allows young people to travel much more than their parents and grandparents, they spend far more time and money at restaurants, and they are less prone to physical activity, which all together affect health (64).

During the last 20 years lifestyle surveys have focused on health behaviours and lifestyle changes that may improve health, such as smoking, alcohol consumption, dietary habits and physical activity (65).

1.4.1 Diet

The modern diet in most westernised countries differs considerably from that of previous generations, in which the prevalence of allergy was significantly lower (66). Nowadays, the diet is dominated by food that has been processed, modified, stored and transported long distances (66). This is in contrast to the traditional diet, which compromise food that was produced and marketed locally and was eaten shortly after harvesting (66). Changing diet, as an explanation of trends in atopic disorders, may not only have a microbial effect by altering the gut flora, but also have biological plausibility via the nutrients needed for healthy immune system development, such as polyunsaturated fatty acids (PUFA) and antioxidants (67).

A large change in the type of fat consumed have occurred in western populations with an increase in the intake of omega-6 family of PUFA, mainly as the plant-derived linoleic acid, and a decrease in omega-3 PUFA found in especially in fatty fish like salmon, herring, tuna and sardines, and fish oils (68). The long chain polyunsaturated fatty acid (LCPUFA), arachidonic acid (AA) (20:4 n-6) is the precursor for the synthesis of prostaglandin E_2 (PGE_2) and thromboxanes (via cyclooxygenase enzymes) and 4-series leucotienes (LTB_4) (via 5-lipooxygenase enzymes), which are mediators of inflammation (68). In addition to pro-inflammatory effects, PGE_2 exerts effect on the Th1/Th2 balance, decreasing the production of the Th1-type cytokines interferon gamma (IFN-γ) and IL-2, and enhancing the production of Th2-type cytokines IL-4 and IL-5, promotinging IgE syntesis by B cells and allergic reactions (69). Increasing consumption of omega-3 LCPUFA results in their incorporation into cell membranes. This incorporation occurs largely at the expense of AA, so decreasing the availability of the substrate for prostaglandin E_2 formation. Thus, it has been proposed that omega-3 LCPUFA will be protective towards allergic disease (70). However, there is conflicting evidence on the use of omega-3 and omega-6 supplementation for prevention of allergic diseases (71).

Probiotics are live microbial organisms that are administered in foods or supplements which in adequate doses confer a health benefit on the host (72). Recent studies have demonstrated reduction in abdominal pain and bloating when treating patients with specific species of *Lactobacillus* and *Bifidobacteria* (72; 73). However, the impact of probiotics in IBS remains unclear, and well designed studies paying attention to both clinical outcome and mechanistic aspects are required (73).

A common dietary advice for patients with IBS, namely supplemental fibre, has come under fire (74). These carbohydrates are incompletely or not digested in the small intestine, but are partly or totally fermented in the large bowel (74). Recent studies indicate that such malabsorption of undigestible but fermentable carbohydrates may be poorly tolerated by patients with IBS and subjective food hypersensitivity (75). A recent study by Austin *et al.* (76) showed that a very low-carbohydrate diet (20g/d) improved symptoms and increased quality of life (QoL) in patients with diarrhoea-predominant IBS. The typical American diet provides approximately 300g of carbohydrates a day. FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols), a term introduced by Gibson and Shepherd (77), are short-chain carbohydrates and sugar alcohols (such as sorbitol and mannitol) widespread in the diet. These compounds have three common functional properties; they are poorly absorbed in the small intestine, are osmotically-

active molecules, and are rapidly fermented by the bacteria in colon, inducing abdominal distension and discomfort in many people, especially those with IBS (77). Gibson and Shepherd showed that a low FODMAP diet provided good relief of symptoms in 75% of patients with functional GI disorders, but further studies are needed to clearly define FODMAD-rich and FODMAP-poor foods, and the cut-off levels of FODMAP contents, which dictates whether the diet is classified as high or low (77).

Peppermint oil may be effective in IBS patients due to smooth muscle relaxing properties (78), but despite numerous reviews on this subject, it is very difficult to give general dietary advice (79). Foods undoubtedly precipitate symptoms in many patients with subjective food hypersensitivity and IBS; but the precise mode of action remains unclear and many vary from one individual to another, and there is doubt that diet can be used solely in the treatment of IBS (80).

1.4.2 Quality of life

The term quality of life (QoL) is used in a wide range of contexts to evaluate the general well-being of individuals and societies (81). The World Health Organization Quality of Life Group, a worldwide research group organized by the World Health Organization, defines quality of life as individuals' perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns (82). The term health-related QoL is often used to indicate QoL as it relates to diseases or treatments (83). Thus, QoL is a broad-ranging concept that incorporates individuals' physical health, psychological state, social relationships, personal beliefs, and their relationship to salient features of the environment (84) (Figure 7).

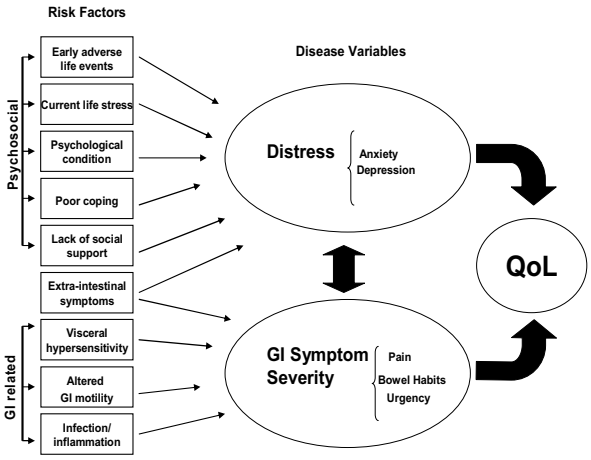

Figure 7. Conceptual model of risk factors and disease variables related to health-related QoL in functional gastrointestinal disorders (84).

Research studies are beginning to identify some of the factors that influence QoL in IBS (85-87). What determines how much IBS affects QoL are the frequency and severity of symptoms, having other medical conditions along with IBS or presence of multiple non-GI physical symptoms, and depression (85-87). Patients with mild IBS may not have worse overall QoL than the general population (88).

1.5 PSYCHOLOGICAL FACTORS

1.5.1 Subjective health complaints

Subjective health complaints (SHC) are referred to as "unexplained symptoms" or complaints without objective pathological findings (89). The main categories of SHC are musculoskeletal complaints, "pseudoneurological" complaints like fatigue, tiredness, dizziness, vertigo and headaches, and GI complaints like pain, bloating and diarrhoea (89). The complaints are normal everyday complaints, and most of us do not seek medical assistance for these conditions. However, health care consumption is significantly associated with SHC, and for some individuals they reach a threshold where sick leave is necessary (90). Medically unexplained symptoms are associated with high rates of disabilities, and the management of the symptoms is perceived as unsatisfactory from the perspective of both the patients and the physician (90).

In our society, a variety of subjective illnesses with few or non objective findings have appeared under different labels for years (91). Examples are chronic fatigue syndrome, fibromyalgia, burnout, food hypersensitivity, chronic low back pain, and multiple chemical sensitivity (92). Paul Briquet`s work from 1859 was the first description of patients feeling that they had been sickly most of their life, and complained of multiple symptoms referable to numerous different organ systems (93). The patients were often fatigue, and they claimed pain in the chest, arms, and legs. In addition, GI symptoms were common, especially bloating and nausea (93). The etiologic factors were youth, female sex, family history of the disorder low social class, and poor physical health, which are the same as those identified to day for SHC (94).

As many as 96% of the general Norwegian population and 75% of the Nordic European countries report some SHC during the last 30 days (95). The definition of subjective food hypersensitivity is analogous to the general definition of SHC, and consistent with recent recommendations where non-toxic adverse reactions to food are referred to as food hypersensitivity (3; 94). Without objective criteria for judgement, diagnostics become difficult and controversial (90). Nevertheless, the patients still have pain or discomfort and feel in need for help and treatment (90). In Norway, almost 50% of sick leave is based on subjective statements from the patients, with few or no objective findings (96). The majority of these complaints are related to muscle and joint pain, but GI problems are also very common (96). Eriksen and Ursin suggest that these complaints are based

on sensations from what usually are normal physiological processes. Furthermore, they suggest that sensitization is the psychobiological mechanism explaining the individual differences in tolerance and acceptance of common health complaints (97). van den Bergh *et al.* (98) argue that medically unexplained symptoms and syndromes may promote two extreme positions. One is that some specific explanatory mechanisms of dysfunction in the body must exist that has yet to be discovered. The other assumes that such symptoms are mainly the result of perceptual-cognitive processes, strengthening bodily sensations resulting from stress and anxiety (98). Cognitive-emotional sensitisation is supposed to be common in medically unexplained somatic complaints, and may even play a role in the aetiology of the complaints (94; 99).

1.5.2 Sensitisation and somatisation

Sensitisation is defined as increased reactivity to stimuli in pain pathways, and visceral hypersensitivity is the exaggerated experience of pain in response to mildly painful or even normal visceral stimuli (99). Generally, sensitisation is caused by an increased efficiency in the synapse due to repeated use, in particular following irregular and extreme stimulation (99; 100). Sensitisation constitutes a feed-forward mechanism, helping the individual to react more efficient in situations with increased probability of harm (99). Sensitised persons are continuously scanning the environment for offending agents. They are also constantly worried about their condition and doing their best to avoid situations to which they attribute their problems (101). Those who have an extreme concern may develop a cognitive bias for information related to somatic disease. They over-report the somatic sensations and misattribute or over-interpret ambiguous information in terms of their illness beliefs (99), and because emotional information often gets processing priority, it causes interference in the processing of other information (99).

According to Brosschot (99), cognitive bias is a higher form of cognitive-emotional sensitisation, or simply cognitive sensitisation. Sensitisation, defined as an increased reactivity to stimuli, has been postulated as the underlying mechanism for somatisation disorders (99-101). Somatisation may be viewed as a psychological or behavioural trait, seen as the propensity to experience and report somatic symptoms, to misattribute them to disease, and to seek medical attention for them (99). Alexithymia, enhanced fantasy life and difficulties in differentiating one`s feelings and expressing them in words, have been associated with somatisation and depressive disorders (102-104).

1.5.3 Stress

The definition of stress has been source for discussion and disagreement among researches for years (105). The Cognitive Activation Theory of Stress (CATS) (106) views the stress as an alarm reaction operating whenever the organism registers that there is a discrepancy between what is expected and what really exists (106). According to CATS (106), physical demands and psychological characteristics that produce the stress response have nothing in common (107). All stimuli are filtered or evaluated by the brain before they gains access to the response system. The main ‘‘filters’’ are related to stimulus expectancy (what does the stimulus mean?) and to response outcome expectancy (what can I do about the stimulus?) (106). The stress response is a part of our biological inheritance, and it affects endocrine, vegetative, immune system, and biochemistry in the brain (106). The alarm, or stress response, depends on both the individuals` experience with the stressor, and the experiences of dealing with the stressor, in any particular situation (106). In other words, it is the individual’s experience of the demands and the expectancies of the outcome, which determine whether the stressor or the demands will cause stress responses. If sustained, they may cause illness and disease in man and animals (106) (Figure 8).

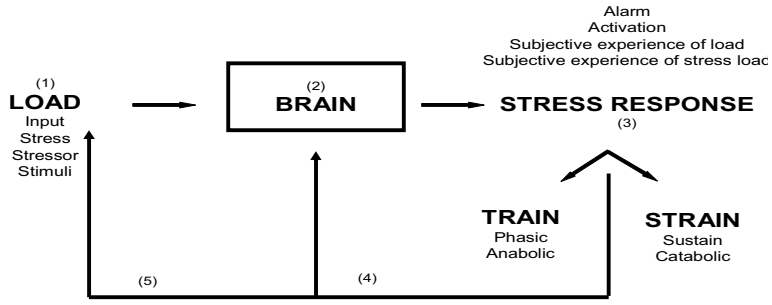

Figure 8. The main aspects of CATS. The load (1, stressor, stress stimuli) is evaluated by the brain (2) and may result in a stress response (3, alarm) that is fed back (4) to the brain. The physiological stress response may lead to training or straining, dependent on the type of activation. Phasic arousal is seen in individuals with a positive expectancy. Sustained arousal may lead to pathology (strain). The brain may alter the stimulus (5) or the perception of the stimulus, by acts or expectancies (106).

Traditions for assessing the role of stress in disease risk are focusing on environmental events or experiences that are "objectively" associated with substantial adaptive demands and on individuals` "subjective" evaluation of their abilities to cope with the demands (108). The Karasek`s Demand/Control model is an "objective" model where a combination of high psychological demands and low task control and skills used at work may predict stress-related ill health behavioural (108). Whether a person's job is perceived as stressful depends on work environment, social support, feeling of being in control of the situation, and coping mechanisms (105; 108). Previous studies have shown that job stress is often associated with heart disease, musculoskeletal pain and depression (108; 109). Jobs with high demands and low control carried the highest risk of illness and disease (110). Control refers to the possibility of using one's own discretion and having authority on how to perform work (110). Low psychological demands and high levels of control carried the lowest risk of illness and disease. Jobs with high demands and high control, and opposite, with low demands and low control carried an average risk (110) (Figure 9).

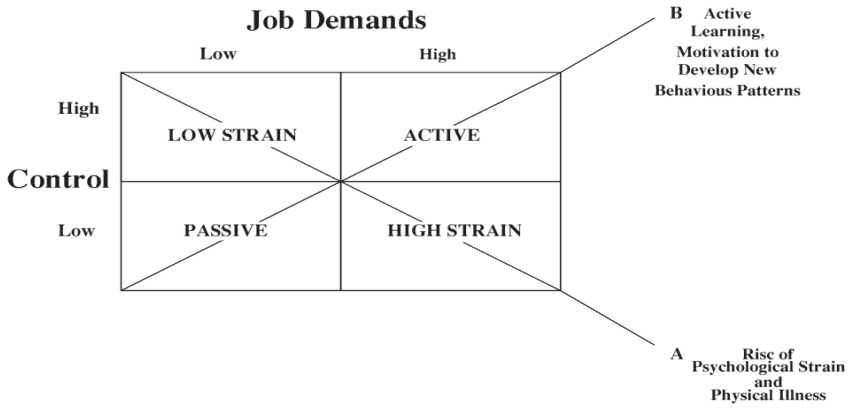

Figure 9. The Demand/Control model propose that job strain results from a combination of high psychological demands with little freedom to make decisions affecting work (e.g., low control). The resulting job strain increases the risk of disease. By contrast, if high demands are combined with high levels of involvement, the stress can be positive, stimulating active learning and personal development (110).

Taché *et al.* (111) suggest that all kinds of stress release corticotrophin releasing factor (CRF), which acts upon the central vagal motor nucleus to suppress efferent vagal activity. This activity evokes widespread autonomic changes, including depression of gastric motility and increased colonic transit time (111) (Figure 10), which means that both gastric emptying and the stomach's ability to adapt to a new volume without an increase in pressure are impaired (111). Impairment of the reflex might be a reason why meal related epigastric discomfort is generated in patients with functional GI disorders (112). CRF receptors are found not only on neurons but also on different immune cells including macrophages, lymphocytes and mast cells. When activated, histamine and other mast cells-derived factors may cause vasodilatation in human skin (113). Recently, Alonso *et al.* (114) reported that chronic life stress may predispose to gut mucosal inflammation in healthy women. The abnormal epithelial response was characterized by an enhanced permeability to antigenic macromolecules. In susceptible individuals, excessive stress exposure is suggested to predispose these persons to develop a new disease or to exacerbate a previous existing one, which may be the case of IBS in women (114).

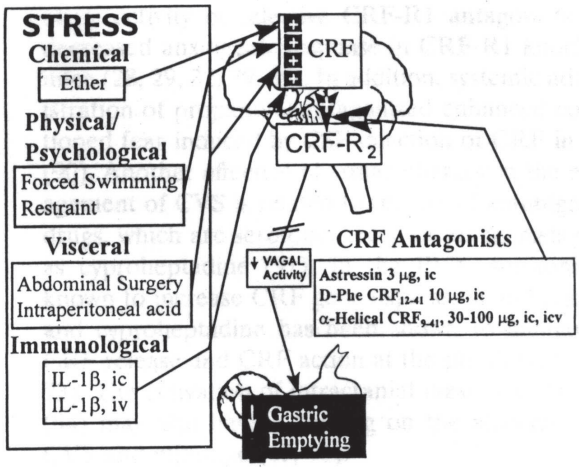

Figure 10. Various stressors induce inhibition of gastric emptying and stimulation of colonic motor function (111)

1.5.4 Coping

Coping has been defined as strategies (115) and strategy styles (116) used to handle perceived stress. The expectancy of coping success is believed to be the essence of coping (117). According to expectancy theories, behaviour is a function of the expectancies one has and the value of the goal toward which one is working. Three main types of expectancies linked to outcome are described; outcome expectancies, role expectancies and control expectancies (118). Outcome expectancies are referred to as expectancies of improvement or expectancies of usefulness/helpfulness, and how strongly patients believe that therapy will help them get better (116). Role expectancies are defined as patterns of behaviour viewed as appropriate or expected of a person who occupies a particular position (119). Control expectancies are conceptually related to the locus of control concept. Locus of control refers to the belief that a consequence (e.g. getting better) either depends on one's own efforts (internal locus of control) or is controlled by external factors such as fate (external locus of control) (120).

In the psychotherapy context, patients` engagement would be influenced by their control expectancies; positive outcome and efficacy expectancies would facilitate active participation, whereas negative expectancies would predict a rather passive role (116). From a theoretical point of view, patients who actively contribute to a therapeutic change are more likely to improve compared with patients who let the experts do (118) (Figure 11). Coping defined as "positive response outcome expectancies," focuses on the subjective experience of the "coping" person irrespective of situation or outcome, and is firmly based on the theory of activation in explaining the somatic reactions, and ultimately health consequences, to stress (106).

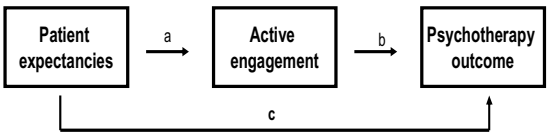

Figure 11. Process model of connections between expectancies, action and outcome (118).

1.5.5 Modern health worries

Over recent years there has been a steady change in the publics` perception of the relation between aspect of modern life and health (121). Concerns about safety of mobile phones, air pollution, vaccines, food additives etc. have led to a heightened awareness of the effect of environmental changes on health (121). Also, popular media now seem to focus more on health threats and highlights toxic and environmental causes of illness that may influence individuals` perceptions of vulnerability to many features of everyday life (122). Research has shown that patients who are most concerned about effects of modern life on health are also more likely to complain of somatic symptoms, have more functional illness, and consume more complementary health care than patients with fewer concerns about modernity (121). Filipkowski *et al.* (122) showed that modern health worries (MHW) were related to the number of SHC and visits to health care providers. Another study suggests that MHW are important psychological factors to consider with regards to attitudes toward functional foods (123). The study of MHW may thus be important for understanding aspects of functional disorders (122).

1.5.6 Biopsychosocial Model

Disease is defined as "the verifiable evidence of a pathological state", while illness is defined as "the patient's perception of ill health, which is symptom reports, perceptions, and behavior" (124). For example, a clinical condition can range from disease without illness (hypertension or asymptomatic ulcer), to illness without disease (fatigue or chronic abdominal pain). In the biomedical model the latter has been labeled as "psychosomatic", a term that question the reliability of the symptoms, even though they are very real to the patient (125).

Thirty years ago Georg Engel (126) highlighted the inadequacies and limitations of the traditional biomedical model and encouraged the development of a biopsychosocial approach. This biopsychosocial approach posits that biological (diseases, genetic dispositions), psychological (thoughts, emotions, behaviour), and social (family, community) factors all play a significant role in human functioning in the context of disease or illness (126). The biopsychosocial model was suggested as a more complete conceptual framework to guide clinicians in their everyday work with patients. The study of every disease should include the associated psychosocial aspects, exemplified in the biopsychosocial model of IBS (125) (Figure 12).

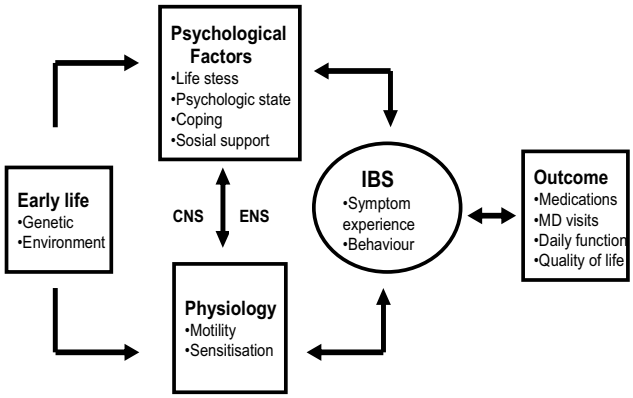

Figure 12. Biopsychosocial Model of IBS. Early life factors influence later psychosocial factors, physiological functioning, their interaction via the CNS/ENS axis and susceptibility to developing IBS. The combined and integrated effects of altered physiology and the person's psychosocial status will affect how the symptom is experienced, the degree of symptom behaviour and ultimately the outcome (taking of medications, physician visits, daily functional status and quality of life). Furthermore, the clinical outcome will, in turn, affect the severity of the disorder (125).

However, the usefullness of the biopsychosocial model has been questioned. Tavakoli thus (127) argues that the biopsychosocial model should be avoided because it promotes an artificial distinction between biology and psychology, and merely causes confusion in psychiatric assessments and training programs. McLaren (128) claims that the biopsychosocial model is neither a theory, nor a model but a “vague, ill-defined, well-meaning froth” masquerading the incomplete understanding of the problem.

1.5.7 Brain-gut axis

The brain-gut axis can be defined as the bidirectional communication between the CNS and the enteric nervous system (ENS) (129). Also, afferent signals arising from the lumen of the gut are transmitted via various visceral afferent pathways (enteric, spinal and vagal) to the CNS. According to the brain-gut axis, the various aspects of IBS symptomatology may be viewed as dysregulation in the complex interplay between events occurring in the gut lumen, the mucosa, the ENS and the CNS leading to alterations in sensitisation, motility and immune function (129; 130). The existence of an extensive brain-immune network suggests that the immune system should be under at least partial influence by psychological processes including learning, psychological stress, emotions, and sensory processes (130). Recent studies also highlight the evidence that intestinal microbiota may be involved in neural development both centrally in the brain and peripherally in the ENS, modulating pain perception and even behaviour (56; 131). Changes in the microbiota, induced by infection or antibiotics, or other event such as stress, which are the strongest risk factors known for the development of IBS, may contribute to inflammation and GI pathology (56). It is possible that disruption or dysregulation of this homeostatic mechanism by stress or infection could affect susceptibility to psychiatric disorders, such as anxiety and depression (132). Taken together, although the psychoneuro-immunologic research over the last three decades has confirmed the existence of bi-directional interactions between the brain and the immune system, the critical question of whether behavioural manipulation, e.g. stressors or intervention, can affect immunity so as to influence health and survival, still remains to be answered (130).

2. AIMS OF THE PRESENT STUDY

The overall objective of this study was to investigate patients with gastrointestinal complaints self-attributed to food hypersensitivity (subjective food hypersensitivity).

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

I Investigate quality of life in patients with subjective food hypersensitivity using the 10-item SF-NDI, after translating and validating the questionnaire to Norwegian.

II Compare the prevalence and severity of SHC and MHW among patients with subjective food hypersensitivity and two groups of controls; health care workers and participants from the general population.

III Compare the lifestyle in patients with subjective food hypersensitivity to an age- and sex matched group of volunteers from the general population.

IV Compare perceived job stress, demands and control in the workplace environment, and the use of specific coping strategies between patients with subjective food hypersensitivity and controls from the general population.

V Examine whether psychological factors such as gastrointestinal symptom-specific and general anxiety and depression could predict symptom severity in patients with subjective food hypersensitivity. For this purpose, the Visceral Sensitivity Index was translated and validated to Norwegian.

3. MATERIAL AND METHODS

3.1 EXPERIMENTAL GROUPS

3.1.1 Patients

Paper I-V: Patients consecutively referred by primary physicians or specialist doctors at Haukeland University Hospital (Bergen, Norway) because of GI complaints self-attributed to food hypersensitivity and age above 18 years were eligible for inclusion in the study. Exclusion criteria were pregnancy or lactating, organic diseases that could explain their complaints, or serious anaphylactic reactions. *Papers I, II, III* include one group, *paper IV* a second, and *paper V* a third group of patients examined between 2001 and 2009.

3.1.2 Controls

Papers I - III: Health care workers, mainly nurses working at Haukeland University Hospital, who were aged 25-62 years and without subjective food hypersensitivity ("healthy controls"), and persons randomly selected from the general population, sex- and age matched to the patients ("population controls") served as control subjects. The health care workers were given written information about the studies and asked to participate. Participants from the general population were contacted after receiving permission from the Norwegian National Registry, using a randomized computer procedure. The persons were mailed a letter explaining the study and questioning whether they would like to participate. Those who gave a positive answer were mailed the questionnaires and a stamped envelope for return mail. The controls were not medically examined, and persons with perceived food hypersensitivity were not excluded. *Papers IV* includes a new group of volunteers selected from the general population following the same procedure as in *paper I - III.*

3.1.3 Ethics

The clinical trials were performed according to the Declaration of Helsinki (133). The Regional Committee for Medical Research Ethics and The Norwegian Social Science Data Services approved the studies. *Paper I – IV*: The patients and controls from the general population gave written informed consent. Controls of health care workers in *paper I - II*, and patients in *paper V* received written information, and gave their consent by returning the filled-in questionnaires.

3.2 MEDICAL EXAMINATIONS

- A complete medical history
- Skin prick tests using 22 common food items and inhalants (ALK Abello, Hørsholm, Denmark)
- Blood samples for determination of serum total IgE and food-specific IgE (CAP-FEIA-System; Pharmacia, Uppsala, Sweden)
- Elimination diet, open provocation, and double-blind placebo-controlled food challenges (DBPCFC) performed by a dietician
- Hydrogen Breath Test (performed to exclude lactose malabsorption)
- Upper gastrointestinal endoscopy, biopsies from the stomach and duodenum (to diagnose Helicobacter pylori infection and celiac disease, respectively)
- Intestinal permeability of 51Cr-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and calprotectin in gut lavage fluid (used for excluding inflammatory bowel disease)
- Microscopy and culture of stool samples (paper I-III) to rule out gastrointestinal infections
- A screening questionnaire (based on Rome II criteria) applied for the diagnosis of functional bowel disorders like functional dyspepsia or irritable bowel syndrome

3.3 QUESTIONNAIRES

Table 2. Overview of study designs

Papers	Study design	Time	Total number of patients	Patients withdrawing	Participants included in the study*	Questionnaires
Paper I	Case-control (MAI 1-2)	2001 - 2003	n=68	n=16 (23.5%)	P=52 C=50 C=70	SF-NDI, GSRS, UESS
Paper II	Case-control (MAI 1-2)	2001 - 2003	n=68	n=16 (23.5%)	P=46 C=50 C=70	SHC, MHW
Paper III	Case-control (MAI 1-2)	2001 - 2003	n=68	n=16 (23.5%)	P=46 C=70	Lifestyle Questionnaire
Paper IV	Case-control (MAI 3-4)	2003 - 2006	n=113	n=17 (15%)	P=64 C=65	SHC, CJSQ, D/C model, UCL
Paper V	Cross-sectional (MAI 5)	2007 - 2009	n=84	n=4 (6%)	P=70	SHC, VSI, HADS, IBS-SQ

*P = patients, C = controls

3.3.1 Short-Form Nepean Dyspepsia Index (SF-NDI)

The 10-item SF-NDI was constructed and validated in patients with functional dyspepsia (134). Subsequently, it was validated in patients with subjective food hypersensitivity (5). The 10-item short form includes five subscales, namely, *tension, interference with daily activities, eating/drinking, knowledge/control*, and *work/study*. Each subscale contains two items. The items a measured on a 5-point graded Likert scale *(1 = not at all, 2 = a little, 3 = moderately, 4 = quite a lot, 5 = extremely)* (134). A total sum score for quality of life and a sum score for each of the five subscales were calculated by adding up scores for each item *(range of total quality of life, 10–50; range of each subscale, 2–10*). Higher scores indicate worse functioning or symptoms (134). The original questionnaire was translated from English into Norwegian, then back-translated into English by two translators. One of them had English as his native language. The two translated English versions were then compared with each other and with the original version, and the authors and the translators came to an agreement of the final Norwegian version.

3.3.2 Gastrointestinal Symptom Rating Scale (GSRS)

The questionnaire includes 15 items and uses a 7-point graded Likert scale defined by descriptive anchors *(1 = no symptoms at all, 2 = minimal symptoms, 3 = mild symptoms, 4 = moderate symptoms, 5 = rather serious symptoms, 6 = serious symptoms, 7 = very serious symptoms)* (135). Higher scores indicate more pronounced symptoms. The items are grouped into five subscales: *abdominal pain syndrome* (abdominal pain/discomfort, sucking sensations in the epigastria, nausea and vomiting), *reflux syndrome* (heartburn, acid regurgitation), *indigestion* (borborygmus, abdominal distension, eructation, increased flatus), *diarrhoea* (increased passage of stools, loose stools, urgent need for defecation), and *constipation* (decreased passage of stools, hard stools, feeling of incomplete evacuation). The original rating scale is interview-based, but it was modified and used as a self-administered questionnaire in later studies (135). A Norwegian version of the GSRS was used in this study (136).

3.3.3 Ulcer Esophagitis Subjective Symptoms Scale (UESS)

The UESS was developed to quantify the symptoms frequently experienced by patients with peptic ulcer and esophagitis (137). The questionnaire comprises 9 items, and a 100 mm Visual Analogue Scale (VAS) is used to quantify the symptoms. The items are grouped into four subscales: *abdominal discomfort* (abdominal pain, sucking sensation), *reflux discomfort* (acid regurgitation, heartburn), *intestinal discomfort* (abdominal distension, borborygmus), and *sleep dysfunction* (difficulty falling asleep, insomnia, rested waking up). Higher scores indicate more pronounced symptoms (137). A Norwegian version of the UESS was used in this study (138).

3.3.4 Subjective Health Complaints (SHC)

SHC were measured by 29 items concerning subjective, somatic and psychological complaints experienced during the last 30 days (89). The degree of each complaint is rated on a 4-point scale *(0 = not at all; 1 = a little; 2 = some; 3 = severe)*. The questionnaire is categorised into five subgroups: *musculoskeletal pain* (headache, migraine, neck pain, arm pain, shoulder pain, upper back pain, low back pain and leg pain), *pseudoneurology* (tiredness, sleep problems, anxiety, sadness/depression, extra heartbeats, heat flushes, and dizziness), *gastrointestinal problems* (gas discomfort, abdominal discomfort, diarrhoea, constipation, gastritis/ulcer, heartburn, and stomach pain), *allergy* (allergies, breathing difficulties, eczema, and asthma), and *flu* (cold/flu and coughing) (89).

3.3.5 Modern Health Worries Scale (MHW)

The scale was developed to assess how concerned the respondents were about the effects of different aspects of modernity on their personal health (122). The MHW Scale has four subscales: *"toxic interventions"* including seven questions on both medical items and vaccination programs as well as dangers seen by individuals in toxic chemicals in household products, *"environmental pollution"* including eight questions about air pollution and depletion of the ozone layer, six questions about *"tainted food"* such as genetically modified food and hormones, additives, pesticides, and antibiotics in food, and finally, *"radiation"* including six items about topics such as radio or cell phone towers and high-tension power lines. Each item is rated on a 5-point scale,

ranging from *"no concern" to "extreme concern"*. The total score is the sum of all 27 questions in the scale (122).

3.3.6 Lifestyle Questionnaire

The questionnaire is similar to one used by the Adventist Health Study at the Loma Linda University Medical Center in California (139). The modified Norwegian version is not formally validated but is cited in previous studies found to work well in patients with GI diseases (136; 140). The questionnaire consists of 72 questions with Likert scores ranging from "1" to "7" or "yes" and "no" for answers. The participants were asked whether they were hypersensitive to coffee, alcohol, orange juice, milk, fried foods, fruit, spicy foods, whole grain bread, tomatoes, fruits, raw vegetables, berries, or other foods. If they answered "yes" to at least one of the questions, they were classified as being food-hypersensitive (136). Furthermore, they were asked about the use of non-steroidal anti-inflammatory drugs during the previous week, rated once per week or more often, and consumption of alcohol during the past year. The patients and the controls were asked whether they were active smokers, ex-smokers, or non-smokers, and for active smokers, the number of cigarettes per day. The remaining part of the questionnaire focused on meal patterns, eating habits, daily intake of fluids, exercise, and sleep during the last month.

3.3.7 Cooper Job Stress Questionnaire (CJSQ)

Job stress was measured using 22 questions of Cooper's Job Stress Questionnaire scored on a 6-point scale grading the amount of stress from 0 *(no stress at all)* to 5 *(a lot of stress)* (141). The questionnaire has four subgroups: *communication* (eight items related to lack of communication, conflicts with management and co-workers, and the relation between different groups of employees), *leadership* (four items related to the employee's relationship to management, the amount of pay, feeling of being undervalued, and the possibilities for promotion), *relocation* (four items referring to how to guide the employees, the stress caused by promotion prospects, relocation and taking work home), and *workload* (five items measuring perceived time pressure, deadlines stress, workload, making mistakes, and stress due to work-influence on private life).

3.3.8 Demand, control and psychological factors in the work environment (D/C model)

Demands and control, and psychosocial factors in the work environment were investigated by 11 and six questions, respectively, from the short Swedish version of psychological demands dimension and the decision latitude dimension from the Demand/Control Model by Karasek and Theorell (108; 142). The demand and control questions are scored on a 4-point scale ranging from 1 to 4 *(1 = no, practically never; 2 = no, rarely; 3 = yes, sometimes; 4 = yes, often)*, yielding a sum score for psychological demands and control. High demands (five questions) are related to working hard and fast, conflict with demands, or insufficient time to work. High scores represent high demands. The six questions on job control are related to task variety, learning new things, and freedom to decide on how to do the work. High scores indicate high control. The questions which examined psychosocial factors in the work environment have response alternatives ranging from 1 to 4 *(1 = failing; 2 = moderate correct; 3 = pretty correct; 4 = correct*). The factors deal with the atmosphere on the workplace, how people take care of each other, and the relationship between leaders and colleagues (108). High scores indicate work well-being.

3.3.9 Utrecht Coping List (UCL)

Coping was examined by the Norwegian short version, the CODE, based on coping strategies from the UCL which consists of 47 statements about how to cope with problems and unpleasant situations (143). In this study we have used 22 of the statements, which implies an instrumental, active, goal-oriented coping style with strategies like *active problem solving* (seven items involving behavioural-like intervention or making several alternative plans), *avoidance and passive* expectancy (eight items implying passivity and avoidance, the problems may solve themselves), and *depressive reaction patterns* (seven items concerning being pessimistic and having a feeling of helplessness, worrying about the past and taking anti-depressive drugs). Each statement is rated on a 4-point scale *(1 = hardly ever; 2 = sometimes; 3 = often; 4 = very often)*. High score on instrumental mastery oriented coping is attained by high scores on active problem solving and low scores on avoidance and passive expectancy and depressive coping (144). Individuals with a high score on this factor do not avoid difficult situations and look at the problem as a positive challenge (143).

3.3.10 Visceral Sensitivity Index (VSI)

The VSI is a 15-item self-report gastrointestinal symptom-specific anxiety questionnaire comprising five dimensions of gastrointestinal-related cognition and behaviours: worry, fear, vigilance, sensitivity and avoidance (145; 146). Item generation is based on considerations regarding stimulus origin as well as affective, cognitive, or behavioural manifestations of the dimensions. The items are ranged from *1 = strongly agree* to *6 = strongly disagree,* but are reverted *(i.e., 1-6 becomes 5-0)* so that high scores indicate high symptom-specific anxiety (146). The questionnaire yields a range of possible scores from 0 (*no gastrointestinal-specific anxiety*) to 75 (*severe gastrointestinal-specific anxiety*). The original questionnaire was translated from English into Norwegian, then back-translated into English by two translators. One of them had English as his native language. The two translated English versions were then compared with each other and with the original version, and the authors and the translators came to an agreement of the final Norwegian version.

3.3.11 Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-assessment mood scale consisting of 14 items, 7 for the HADS-A (anxiety) and 7 for the HADS-D (depression) (147). Each item is rated from 0 *(not present*) to 3 *(maximum)*. The scale has been extensively validated and is well accepted in both psychiatric and non-psychiatric settings (148). In this study, two groups of psychopathology were defined: case level anxiety (HADS-A $\geq$ 8) and case level depression ((HADS-D $\geq$ 8), which is based on commonly accepted cut-off values on HADS (148).

3.3.12 Irritable Bowel Syndrome Symptom Questionnaire (IBS-SQ)

The questionnaire IBS-SQ examines the severity of six gastrointestinal symptoms: nausea, bloating, abdominal pain, diarrhoea, constipation and anorexia, and is rated on a scale from 0 (*no symptoms)* to 10 (*severe symptoms)* (149).

3.4 STATISTICS

3.4.1 Psychometric properties of questionnaires

Reliability is the extent to which a measure is stable or consistent and produces similar results when administered repeatedly (150; 151). In paper I and V test-retest reliability was determined by both limits of agreements according to Bland and Altman (150), and Pearson correlating test after administering the questionnaires to the same persons 4 weeks apart. If the correlation between separate administrations of the test is ≥ 0.7, then it has good test-retest reliability (150; 151). Bland and Altman's plots for limit of agreement (useful when there are only two raters) is to calculate the mean of the differences between the two raters (151). The confidence limit around the mean provide insight into how much random variation may be influencing the ratings (151). Cronbach alfa, which was used in the Norwegian version of the VSI in paper V, is a coefficient (a number between 0-1) that rates the internal consistency or reliability of items in the questionnaire. A test has a strong internal homogeneity when correlation among items is ≥ 0.7 (152).

Validity is the degree to which an instrument measures what it is intended to measure (150; 151). There are two main forms of validity: *internal and external validity. Internal validity* refers to the internal structure of a questionnaire and may be done in four different ways; factor analysis, convergent and discriminant validity, and floor–ceiling effects (150; 151). Factor analysis, which was used in paper V, is a statistical method that describes variability among observed variables in terms of fewer unobserved variables called factors. *External validity* is the relationship between the test and the external criteria such as other measures of the same or other dimensions of the measurement, and is measured by face, content, construct and criterion validity (150; 151). In paper I and V we used face validity, which denotes whether the questions "make sense", and is assessed by having patients and "experts" reviewing the contents of the questionnaire to see if the items seem related to the topic that is going to be investigated. In paper I construct validity, reflecting the ability of an instrument to measure an abstract concept or construct, and the extent to which a measure under investigation provides results that are consistent with the theories that are assessed, was evaluated by correlating scores in the SF-NDI with scores in the GSRS and UESS. Known-groups validity is a form of construct validation in which the validity is determined by the degree to which an instrument can demonstrate different scores for groups known to vary on the variables being measured (150; 151). In paper V this validity were done by correlating VSI with patients reporting IBS-SQ scores < 25 and IBS-SQ scores ≥ 25, and HADS-A scores <8 and HADS-A scores ≥8. We also used concurrent validity, evaluating the degree to which two or more measures

that theoretically should be related to each other, in fact, observed to be related to each other, correlating VSI and HADS-A.

Responsiveness is the ability of an instrument to detect clinically important changes (153). There are two major aspects of responsiveness, the *internal responsiveness* that characterizes the ability of a measure to change over a particular specified time frame, and the *external responsiveness* which reflects the extent to which changes in a measure over a specified time frame relate to corresponding changes in a reference measure of health status (154). In paper I, responsiveness was tested by correlating changes in SF-NDI total score over 4 weeks with the corresponding symptoms changes in GSRS total score.

3.4.2 Statistics (Paper I-V)

All statistic calculations and graphic designs were performed using the Graphpad Prism 4.0 and 5.0 (GraphPad Software Inc, San Diego, USA) and SPSS 16.0 for Windows (SPSS Inc., Chicago, IL) statistical software package. The values are given as mean ± SD (paper I, III IV and V) and median with interquartile range (paper II and III) according to distribution of data. Differences between means were calculated with parametric tests for data normally distributed, and non-parametric tests for data not normally distributed. Pearson`s correlation coefficient was used for correlation analysis. Influence of psychological factors on somatic symptom severity was studied by multiple regression analysis**.** All tests were two-tailed, and $P < 0.05$ was chosen as the level of statistical significance.

Differences between groups were evaluated using:
Paper I: One-way ANOVA and unpaired *t* test
Paper II: Kruskal-Wallis test and odds ratios (OR), with 95% confidence interval (95% CI)
Paper III: Chi-square test and OR (95% CI) and unpaired *t* test
Paper IV: Unpaired *t* test, OR (95%CI), and Fisher`s exact test
Paper V: Unpaired *t* test

4. SUMMARY OF RESULTS

4.1 PAPER I

Quality of Life in Patients with Subjective Food Hypersensitivity: Applicability of the 10-Item Short Form of the Nepean Dyspepsia Index

The patients (n = 52) reported poor quality of life compared with controls of health care workers (n=50), (P<0.001) and participants from the general population (n = 70), (P < 0.001). The SF-NDI provided reliable, responsive, and clinically valid measures of quality of life in these participants. Scores on SF-NDI were significantly correlated with scores on the GSRS (r = 0.34, P = 0.02) and UESS (r = 0.41, P = 0.003). Food hypersensitivity was confirmed in four patients, and the quality of life impairment was similar in the patients who had verified compared to those who had subjective food hypersensitivity. Thirty-four (65%) of the patients reported having atopic disease (rhinoconjuctivitis, atopic dermatitis, urticaria, asthma, and/or oral allergic syndrome) in addition to the food hypersensitivity.

4.2 PAPER II

Subjective Health Complaints and Modern Health Worries in Patients with Subjective Food Hypersensitivity

The patients (n = 46) reported more frequent and severe health complaints than healthy controls (n = 50) (P < 0.0001) and volunteers from the general population (n = 70) (P < 0.0001). The patients scored significantly higher than controls on sum scores for four domains of the SHC including gastrointestinal complaints (P < 0.001), musculoskeletal complaints (P < 0.01), “pseudoneurology” (P < 0.001), and allergy (P < 0.001). Total sum scores on the MHW scale did not differ significantly among the groups. The patients were significantly more worried about overuse of antibiotics (P < 0.001), amalgam in dental fillings (P < 0.01), and additives in food (P < 0.05), and genetically modified food (P < 0.05). None of the patients had IgE-mediated food allergy according to generally accepted definition (40). Two patients had non-IgE mediated food

hypersensitivity to egg and yeast/wheat flour, respectively, with a positive DBPCFC but a negative skin prick test and/or specific IgE in serum.

4.3 PAPER III

Lifestyle of Patients with Self-Reported Food Hypersensitivity Differ Little From Controls

All (n = 46) of the patients and 43% (n = 30) of the controls reported adverse reactions to one or more foods (P = 0.0001). The patients reported intolerance to a mean of 4.0 (range 1–9) food items compared with 2.0 (range 1–3) among the controls. Except for coffee, a significantly greater part of the patients reported hypersensitivity for all the 12 food items mentioned in the questionnaire. Fruits, milk, orange juice, and raw vegetables were the most common foods to which the patients reported intolerance. The controls avoided fruits, coffee, orange juice, and spicy foods. In the category "other foods" causing intolerance, the patients reported wheat and eggs compared with the controls who reported peanuts and fatty foods. Significantly fewer patients (72%) than controls (94%) reported use of alcohol the last year (P = 0.008). Eating habits, meal patterns, hours of sleep per night, the amount of exercise per week, and use of painkillers during the last month were similar in both groups.

4.4 PAPER IV

Job stress and coping strategies in patients with subjective food hypersensitivity

Compared to controls (n = 65), patients (n = 64) scored significantly lower on job stress (P = 0.01) and job demands (P = 0.04), and significantly higher on authority over job decisions (P = 0.04). Generally, the participants were satisfied with the work environment, and they reported similar active coping pattern like the controls scoring high on instrumental mastery oriented coping; high on active problem solving and low on avoidance and passive expectancy and depressive coping. The patients reported significantly more SHC than the controls (P = 0.0001) where the five most dominant complaints were: gas discomfort (95%), diarrhoea (86%), stomach discomfort (84%), tiredness (84%) and headache (69%). The main complaints in the control group were tiredness (71%), headache (69%), neck and low back pain (51% and 46%, respectively) and gas discomfort

(48%). Patients (44%) working part time reported significantly more SHC than those who were full time employed ($P = 0.0005$). In the control group, there was no such significant difference. None were diagnosed as having celiac disease or any other organic GI illness. IgE-mediated allergy to egg was diagnosed in one patient and non-IgE-mediated allergy to wheat flour in another. Forty-nine (76.5%) of the patients were diagnosed having IBS according to the Rome II-short criteria.

4.5 PAPER V

Do psychological factors predict symptom severity in patients with subjective food hypersensitivity?

The study included 70 patients with subjective food hypersensitivity. In the multiple regression analysis neither GI nor non-GI symptom severity were significantly correlated to scores on psychological factors when these were considered together, $P = 0.08$ and $P = 0.68$, respectively. Adding age to the model, increased the amount of explained variance in non-GI symptom severity from 2.2% to 11.3% ($P = 0.10$), while the amount of explained variance in GI symptom severity remained unchanged (9.4%, $P = 0.16$). In the final model (including age), the VSI was a significant predictor for GI symptom severity ($P = 0.02$), but not for non-GI symptom severity ($P = 0.48$). Age was the sole significant predictor of non-GI symptom severity ($P = 0.01$), whilst GI symptom severity was not predicted by age ($P = 0.85$). One patient had positive skin prick test (in addition to elevated serum specific IgE) for one food allergen (wheat). However, DBPCFC could not confirm food allergy in any of the patients. Among the 70 patients included, 66 (94%) had IBS according to the Rome II criteria. The Norwegian version of the VSI had satisfactory validity.

5. GENERAL DISCUSSION

5.1 QUALITY OF LIFE, SUBJECTIVE HEALTH COMPLAINTS AND MODERN HEALTH WORRIES (PAPER I AND II)

We rarely found indications of food allergy in patients with GI complaints self-attributed to food hypersensitivity. This is consistent with the findings of others (155; 156). When the food hypersensitivity remained unexplained following a structured medical work-up, we denoted the condition subjective food hypersensitivity (5). More than 90% of these patients presented with IBS-like symptoms. Bloating, abdominal pain and altered stool pattern were the most prominent symptoms (5; 157). However, many patients also reported a number of non-gastrointestinal symptoms such as fatigue, anxiety, depression, musculoskeletal pain and sleep disorders (6), and some patients felt "sick all over".

Compared with controls, the patients reported considerably impaired QoL (5). This is in accordance with previous studies of people suffering from perceived food hypersensitivity and IBS (158; 159). Spiegel *et al.* (160) recently evaluated the determinants of both mental and physical health related QoL in 770 IBS patients recruited both by advertisement and as tertiary referrals at a university-based centre. Fatigue, low "energy", painful symptoms, feeling nervous and hopeless were factors influencing their QoL (160). Several studies have reported that these patients also contact general practitoners, medical specialists, and alternative healers more frequently than the general population (1; 53; 161). Research is most often conducted in hospital settings, but also in population-based studies (162) people with food hypersensitivity and IBS experienced significant impairment in health related QoL compared with population-based controls.

Generally, IBS patients report QoL impairment that is equal or greater than that seen in individuals with asthma, migraine or gastroesophagal reflux disease (158). Even compared with serious chronic conditions like diabetes mellitus and end-stage renal disease, the IBS patients report lower values in several aspects of QoL (159). Consistent with our findings, numerous co-exiting symptoms seem to be particularly associated with worse QoL (87). The impact of functional GI disorders on QoL is often underestimated by health care workers because people with these disorders do not face direct threat to their life and are not disabled in any obvious way. For the same reason, friends and family members of individuals with functional GI disorders may underestimate the impact these disorders can have on a person. The Norwegian version of the

instrument for assessment of QoL performed satisfactory in patients with subjective food hypersensitivity (5).

In this thesis, altogether 180 patients and 185 controls (paper II, IV and V) were examined using the Subjective Health Complaint Inventory. The patients reported significantly more SHC from different organ systems compared with controls, especially GI complaints, and anxiety and depression. There is an extensive literature relating IBS and other medically unexplained physical symptoms, including subjective food hypersensitivity, to anxiety and depression. However, to what extent psychological factors explain symptom severity in the patients is still not clear (7; 163; 164).

The majority of our patients were offended when the possibility of psychological factors, as a contributor to their complaints, was discussed (165). That patients often form own ideas about their illness (166), which may lead to a vicious circle in which somatic causal assumption leads patients to be more preoccupied with their bodies and more aware of their symptoms. Patients with verified food allergy are often well safeguarded by the health care workers, while the majority with unexplained functional disorders often feel that they are neglected and therefore forced to seek help from alternative medicine (167). There it may be easier to get a "diagnosis" and accept for their ideas about their illness, but in many cases alternative treatment usually has short-lasting effect and can be very expensive for the patients (168; 169). Many patients know that presenting IBS-like symptoms does not result in much help from physicians or other health care professionals (61). Some physicians even deny the very existence of the functional GI disorders, whereas others show dismissive or negative attitudes toward patients (170; 171). On the other hand, rather than being relieved to hear that "nothing is wrong", patients may become angry, and even resentful, and demand further tests, which may pursue unnecessary diagnostic studies to find something "real" (172), resulting in increased health care costs and possibly inappropriate care (173).

It has been argued that the boundaries of medically unexplained symptoms largely coincide with the current limits of medical knowledge (174), and diseases outside these limits are often given psychiatric explanations, like somatisation disorders. At once the physician even "knows" what caused all the symptoms, which is in fact rarely the case in somatic medicine. Also, the "resistance" against the diagnosis is often taken as confirmation that it is correct, which according to our experience often is the case in subjective food hypersensitivity patients. Also, a diagnosis of somatisation may not be an innocuous label because it may close various doors and lead the planning of treatment into track that may gets nowhere (174).

A large body of research has documented the role of stressful life events and repeated or chronic environmental challenges in vulnerability to illness (175), and the tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them is a widely accepted concept. When there is a circular relationship between different causal factors, it is difficult to know what the cause of the symptoms is. In the end, we are all biological beings, and further studies are eagerly needed to resolve whether the psychological factors are the cause or consequence of IBS, or whether they are simply parallel manifestation of an underlying disorder.

MHW have been associated with SHC and health care use (176). However, in the current study, the patients did not report more MWH than controls. Our patients with subjective food hypersensitivity were concerned about specific food items, not about food in general or, for instance, the influence of modern life on health. Hence, MHW seems to have no influence on the number or severity of SHC reported by our patients. The participants` age may influence the results. A previous study utilizing a more diverse age range found that older individuals reported less concern regarding modernity than younger persons (177). Furthermore, the patients` strong assumptions with regards to the cause of their symptoms may also play an important role in the low scores on the MHW scale.

6.2 LIFESTYLE, JOB STRESS AND COPING STRATEGIES (PAPER III AND IV)

The lifestyle of patients with subjective food hypersensitivity differed little from controls, which is consistent with other quantitative studies about lifestyle in similar patient groups (178; 179). Peveler *et al*. (179) found that 12% of people with perceived food hypersensitivity reported moderate or great influence on activities of daily living such as housework, social life, eating out, and physical activity, while Knibb *et al*. (178) reported that 17% of the food-intolerant interviewers attributed effects on lifestyle. In qualitative research, however, patients reporting food hypersensitivity and IBS often claim considerable influence on lifestyle, especially on dietary ingredients and meals, stress, sleep and physical activities in efforts to improve symptoms (180; 181). In a study by Jarret *et al.* (180), women with subjective food hypersensitivity and IBS developed self-care strategies including eating once a day, fasting for short periods or having small meals in non-stressful situations. The women spent quite a lot of time identifying offending food, still the process was not always successful. Very few patients, only four percent, sought dietary advice from physicians, dieticians or nurses (178), perhaps because they knew that the health care professionals could not help. Many patients felt quite helpless because of the infrequent and unpredictable symptoms (180).

None of the included patients had lactose malabsorption or positive DBPCFC with milk, still significantly more patients than controls offended milk. A possible explanation may be that many patients had been told, from childhood, that they were intolerant to milk, which may have convinced them that milk is the cause of their food hypersensitivity. In our study less patients than controls used sweets, coffee, and alcohol, which are known to cause gastrointestinal symptoms in some sensitive individuals (79; 80). Interestingly, there were no difference between patients and controls in consumption of fermentable whole-grain bread, fruits, and raw vegetables that recently have been implicated in symptom generation in patients with IBS (79). This may be due to lack of knowledge or because the Norwegian health authorities insist that such food items are healthy and beneficial (182).

The fact that 43% of the controls reported hypersensitivity to at least one food item may be due to an increased prevalence of food hypersensitivity in the general population (183), or because of the public and medical interest in the topic. Clearly, this high prevalence of perceived food hypersensitivity in the general population makes it difficult to document differences between patients and controls. The controls were not medically examined; therefore, we do not know

whether their perceived food hypersensitivity represent a real allergy or not. The results from the questionnaires indicate that the controls perceived themselves as more healthy than the patients, reporting a better QoL and significantly fewer SHC than the patients. Nevertheless, the patients and controls slept on average the same number of hours per night, and their exercise pattern and use of pain killers were similar. One explanation may be that about 40% of the patients experienced that exercising improved their symptoms, which may cause better sleep.

It is well known that stress may aggravate GI disorders (54; 180) and may also play a role in the pathogenesis of hearth disease, musculoskelestal pain and depression (109; 110). Whether a person's job is perceived as stressful depends on work environment, social support, feeling of being in control of the situation, and coping mechanisms (105; 108). Karasek (108) hypothesise that high job demands and low control carries the highest risk of illness and disease did apparently not imply to our patients who reported significantly lower scores on job stress and significantly higher scores for authority on job decision and control than the participants from the general population. Furthermore, the patients and controls were equally satisfied with their job environment. Jones *et al.* (184) showed that the dominant coping strategies in patients with gastrointestinal complaints such as IBS or inflammatory bowel disease (IBD) were more on escape and avoidance strategies than planned problem solving, but our patients used similar problem-solving coping, e.g., positive response expectancies like the controls. The results suggest that job stress and coping strategies have a weak impact on patients with subjective food hypersensitivity and IBS. One explanation may be that patients who report adverse food reactions are mostly women (6; 185), often being part-time workers. Nearly half of the patients (44%) and 32% of the controls worked 50% of full time, which may contribute to less perceived job stress in general (92; 97). Another explanation may be that the patients` somatic complaints, especially the GI complaints, prevented them from seeking stressful jobs or leading positions.

6.3 ROLE OF PSYCHOLOGICAL FACTORS (PAPER V)

In the fifth paper we investigated whether psychological factors such as symptom-specific and general anxiety, and depression could predict somatic symptom severity in patients with subjective food hypersensitivity and IBS. The presence of multiple co-morbid disorders has been suggested as a marker for psychological influences on etiology (186). In the present study, 24% of the patients reported anxiety and 14% depression on the HADS questionnaire, which is in accordance with a previous study of a similar patient material were anxiety disorders (34%) and depression (16%) were the predominant psychological factors (163). In the present study, however, psychological factors explained, when considered together, only approximately 10% of the variance in the patients` symptom severity; hence, 90% of the variance remained unexplained.

Stress and negative expectancies are, in general, assumed to be causally related to symptom severity and to play an important role in the development of multiple SHC (187). In patients with subjective food hypersensitivity, fear of symptoms after eating a meal could represent a considerable stress factor, in particular, if associated with beliefs of poor symptom control. We therefore made a new questionnaire with 4 negative and 4 positive statements related to more or less unpredictable reactions in response to food intake and coping capabilities (Appendix I, page 71). Dividing sum scores for negative by sum scores for positive expectancies gave an individual "weighted" ratio referred to as the expectancy to food (ETF) score. Interestingly, in our patients positive and negative expectancies almost balanced each other, giving a mean ratio of negative to positive expectancies of (1.3 ± 0.59), not significantly different from 1.0 (unpublished results). The low ETF and weak influence of negative outcome expectancies on symptoms may be related to these patients' strong belief in own attribution and coping capabilities. It is also worth noticing that our patients were free from symptoms during fasting and during the night (unpublished results). These symptom-free periods conceivably provide a window with possibilities of restitution, an important aspect of coping (188), besides being a sound argument favouring the patients' belief that food is the culprit.

ETF scores were strongly correlated to the VSI ($P = 0.0001$), probably because they both measure the same dimension (Appendix II, page 72). As a consequence, we gave the established VSI priority in the regression analysis and the ETF results were not published. However, several things can be learned from our ETF results. First of all, the influence of expectancies on health apparently depends on the balance between negative (hopelessness) and positive (coping) outcome

expectancies as also shown previously (189). This balance is not accounted for by the VSI, which primarily measures aspects of anxiety related to expected symptoms. In the present study, this "gastrointestinal symptom-specific anxiety" was the sole independent psychological predictor of gastrointestinal symptom severity explaining approximately 7% of the variance in gastrointestinal symptoms ($P = 0.02$). The results agrees with prior studies where the VSI was significantly related to the presence and severity of IBS (145; 146; 190), which also indicate that our Norwegian version of the VSI have excellent consistency and reliability (151). The VSI correlated significantly with GI symptoms and general anxiety scores, but general anxiety explained only 1.3% of the variance in GI symptoms, suggesting that general anxiety is even less important for symptom generation than symptom-specific anxiety in these patients. Age was the sole predictor of non-abdominal symptoms, which seemingly were largely unrelated to psychological factors. Hence, our results suggest that the pathophysiology of subjective food hypersensitivity may depend less on psychology and more biology than previously thought.

ETF and VSI are both measures of expectations of symptoms in response to food intake. To call these expectations "symptom-specific anxiety", as done in the VSI, may be a misnomer, misleading the reader to think that anxiety is the primary cause of the problems. Our ETF results suggest, on the contrary, that the symptoms reported by the patients have little to do with anxiety, but rather to reasonable expectancies. The high prevalence of anxiety among patients with subjective food hypersensitivity tells nothing about causality. It may as well be that unpredictable food reactions cause anxiety, or it may be a third, external factor causing both problems independently. Twenty years ago peptic ulcer patients faced a similar problem. Their disease was also associated with a high prevalence of anxiety, and therefore classified as a psychosomatic disorder (191; 192). After the discovery of *Helicobacter pylori,* the diagnosis and treatment of the disease changed dramatically (193), and a 10 years' follow-up study of cured ulcer patients showed complete disappearance of the psychological problems in the near 100% relapse-free patients. Hence, in the case of peptic ulcer disease, the psychological problems were clearly a consequences, not a cause of the disease (194).

A number of recent studies have provided evidence of immune activation (e.g., release of cytokines, histamine, and proteases) in the intestinal mucosa of IBS patients (56; 195; 196)**.** Conditions that are known to predispose to IBS, such as enteric infection, antibiotic use, and stress, may all change the intestinal microbiota (56), which in turn may trigger local and systemic immune activation, low-grade mucosal inflammation, increased intestinal permeability, and disturbances of

intestinal motility and fermentation (197). More than 60% of consecutive patients referred to our interdisciplinary team for evaluation of food hypersensitivity have atopic disease, and these atopic patients have significantly more “IgE-armed” mast cells in their duodenal mucosa and increased intestinal permeability compared with non-atopic patients (198). The clinical significance of this new exciting finding is not yet clear and more research is required to disclose the role of “IgE-armed” mast cells and intestinal permeability in patients who usually have negative DBPCFC, which until now has been regarded as the gold standard for diagnosing food hypersensitivity (26). Interestingly, we have recently shown that joint and bodily pain is attenuated following enteral (tube) administration of seal oil to the duodenum (199). Systemic manifestations (co-morbidities) in subjective food hypersensitivity often regarded as psychiatric somatisation doesn’t fit with a rapid (within 10 days’) effect of seal oil administration, an effect supposed to be due to suppression of prostaglandin E_2 production by the administrated omega-3 PUFA. Earlier, we have shown a similar rapid effect of duodenally administered seal oil in patients with IBD related joint pain (200). The recent finding of increased concentrations of BAFF (B-cell activating factor) in blood and intestinal lavage from our patients (201) supports the concept of immune activation in patients with subjective food hypersensitivity.

Recent articles indicate that IBS patients have normal production of intestinal gas (202), but high concentrations of short chain fatty acids in feces (203; 204). In patients with post-infectious IBS following cure of *Gardia lamblia* infection, total fecal excretion of short chain fatty acids was increased (205). Several of these patients also had increased fecal excretion of fat, indicating intestinal malabsorption (205). A possible mechanism of increased fecal excretion of short chain fatty acids is that the fermenting flora in the coecum is impaired or overwhelmed. Fermentation of carbohydrates may thus continue along the entire colon until the rectum, creating flatulence and abnormal amounts of unabsorbed short chain fatty acids in feces. (Short chain fatty acids are produced of microbial fermentation and normally quickly absorbed from the colon, leaving only around 5% to be excreted). Our working hypothesis is that IBS-like symptoms in patient with subjective food hypersensitivity is due to altered small intestinal motility (stress, allergy), causing malabsorption of carbohydrates, and sometimes even fat (206). Consistently, reducing the demands on intestinal fermentation by a diet low in carbohydrates alleviates the symptoms (207; 208). Further dietary studies are eagerly awaited because an effective treatment could elucidate the unresolved problem of whether psychological factors are the cause or consequence of IBS, or whether they simply are parallel manifestations of an underlying disorder.

6. CONCLUSIONS

6.1 INDIVIDUAL PAPERS

Paper I: Compared with controls the patients reported an impaired quality of life. Validation of the Norwegian version of the SF-NDI questionnaire showed satisfactory psychometrics.

Paper II: The patients reported significantly more SHC than the controls. The patients were concerned about some specific food items, but they did not report more modern health worries than the controls.

Paper III: Lifestyle differed little between patients and controls. The patients reported hypersensitivity to more food items, and they used less milk, coffee and alcohol than the controls.

Paper IV: The patients reported more SHC than the controls, but significantly lower scores on job stress and significantly higher scores for authority on job decision and control. Patients and controls were equally satisfied with the job environment, and they used similar coping strategies for solving problems and difficult situations. The results suggest that job stress and coping strategies have little impact on all the patients` health complaints.

Paper V: The psychological factors explained only 10% of the variance in the patients` symptom severity; hence 90% of the variance remained unexplained. Gastrointestinal symptom-specific anxiety was the sole independent psychological predictor of GI symptom severity, while age was the sole predictor of non-GI symptoms. The Norwegian version of the VSI demonstrated satisfactory validity and reliability.

6.2 OVERALL CONCLUSIONS

The thesis suggests that patients with subjective food hypersensitivity and IBS have impaired quality of life. The patients report more anxiety, depression and SHC from different organ systems compared with controls. On average 90% of the patients present with symptoms consistent with IBS. The small lifestyle differences between patients and controls are most likely a consequence and not a cause of the complaints. Neither lifestyle nor job stress or coping strategies could explain the patients` SHC, and psychological factors explained only approximately 10% of the variance in the patients` symptom severity.

The pathophysiology of these patients' suffering may be more biologic and less psychologic than previously thought. Further interdisciplinary, translational research on food allergy, immune activation, intestinal absorption and motility, and intestinal microbiota are warranted in patients with subjective food hypersensitivity.

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Appendix I

Forventninger til mat

(Expectancies to Food, ETF)

Nedenfor finner du eksempler på utsagn som beskriver hvilke forventninger du har til mat, for eksempel oppblåsthet, forstoppelse, diaré, tidlig metthet, kvalme, magesmerter, tretthet, utslett, muskel-/ledd smerter eller hodepine. Vennligst kryss av ett alternativ for hvert spørsmål.

Spørsmål	***Nesten aldri***	***Sjelden***	***Ofte***	***Veldig ofte***
1. Jeg føler meg stresset av at jeg bestandig må ta hensyn til hva jeg spiser				
2. Jeg vet ikke sikkert hvilken mat som er årsak til plagene				
3. Selv når jeg utelukker mat jeg ikke tåler, føler jeg meg ikke trygg				
4. Det plager meg veldig at reaksjonene på mat er så uforutsigbare				
5. Jeg tror at jeg selv skal klare å finne ut av plagene mine				
6. Når jeg får plager på grunn av mat, vet jeg hva jeg kan gjør for å lindre dem				
7. Når jeg utelukker mat jeg ikke tåler, føler jeg meg trygg				
8. Når jeg er i godt humør, betyr det mindre hva jeg spiser				

APPENDIX II

Questionnaires	**IBS-SQ**			**SHC-Non-GS**		
	R square	*B*	*P-value*	*R square*	*B*	*P-value*
HADS-A, VSI, HADS-D	0.094		0.088	0.022		0.686
HADS-A, VSI, HADS-D, AGE	0.094		0.164	0.133		0.096
HADS-A		-0.322	0.465		0.584	0.103
VSI		0.186	0.024		-0.042	0.513
HADS-D		0.620	0.285		-0.559	0.220
AGE		-0.015	0.850		0.155	0.012

Visceral Sensitivity Index (VSI), Hospital Anxiety Depression Scale (HADS-A and HADS-D)

Questionnaires	**IBS-SQ**			**SHC-Non-GS**		
	R square	*B*	*P-value*	*R square*	*B*	*P-value*
HADS-A, ETF, HADS-D	0.079		0.139	0.052		0.310
HADS-A, ETF, HADS-D, AGE	0.081		0.232	0.128		0.060
HADS-A		0.134	0.734		0.487	0.114
ETF		4.307	0.042		-2.032	0.210
HADS-D		0.260	0.654		-0.441	0.326
AGE		0.029	0.709		0.141	0.020

Expectancies to Food (ETF), Hospital Anxiety Depression Scale (HADS-A and HADS-D)