IS TOTAL IMMUNOGLOBULIN E AND ATOPIC SENSITIZATION ASSOCIATED WITH FOOD-RELATED GASTROINTESTINAL COMPLAINTS?

Ellen Johanne Vara

2014

Institute of Medicine, Faculty of Medicine and Dentistry

University of Bergen

Department of Clinical Medicine, Haukeland University Hospital, Bergen Norway

ACKNOWLEDGEMENTS

ABSTRACT

Background: We have observed increased number of "IgE-armed" mast cells in duodenal mucosa of patients with food hypersensitivity, and therefore we wanted to explore whether serum total IgE levels and atopic sensitization is associated with food-related gastrointestinal (GI) complaints.

Methods: Levels of serum total and specific IgE and GI complaints were measured in 161 patients referred to Section of Clinical Allergology, Haukeland University Hospital, and in a general population sample of 479 persons participating in the Bergen ECRHS. Standard inhalant and food allergens were measured in the patient group, and inhalant allergens of *Dermatophagoides pteronyssinus*, cat and grass were analyzed in the general population sample. All participants filled out two questionnaires, i.e. irritable bowel syndrome (IBS)-Symptom Severity Scale (IBS-SSS) and IBS-Symptom Questionnaire (IBS-SQ), to assess their GI complaints. Statistical analyzes included bivariate analyzes and multiple regression models.

Results: Total IgE was a significant predictor of GI complaints in a total study population (b = .037, p = .001). This was found in the general population (b = .038, p = .005), but did not reach statistical significance in the patient group. Atopic sensitization was inversely associated with GI complaints in both groups, the association was significant in the patient group (b = -77.216, p = .001), but not in the general population. Total IgE and atopic sensitization could together explain 6.2 % of the total variance in GI complaints in the patient group and 1.9 % in the general population. The association of total IgE with GI complaints was consistent among atopic and non-atopic persons, men and women, and across age groups, and no interaction was found by atopic status, sex or age.

Conclusion: Serum total IgE was positively associated with GI complaints, while specific IgE was inversely associated with GI complaints. Together, total IgE and atopic sensitization could explain a relatively small proportion of the total variance in GI complaints. The biological mechanisms of food-related GI complaints involving total IgE, but not specific atopic sensitization, warrants further studies.

CONTENTS

Table V: Multiple regression analysis with GI complaints
(IBS-SQ) in total study population

LIST OF ABBREVATIONS

IgE	Immunoglobulin E
GI	Gastrointestinal
IBS	Irritable bowel syndrome
IBS-SSS	Irritable bowel syndrome - Symptom Severity Scale
IBS-SQ	Irritable bowel syndrome - Symptom Questionnaire
SFH	Self-reported food hypersensitivity
MAI	"Matallergi og Intoleranse (Norwegian translation for food allergy and intolerance)
HUH	Haukeland University Hospital
ECP	Eosinophil cationic protein
CNS	Central nervous system
DCs	Dendritic cells
APCs	Antigen presenting cells
IL	Interleukin
CD38	Cluster of differentiation 38
BAFF	B-cell activating factor
PAF	Platelet activating factor
LDCs	Low-digestible carbohydrates
FODMAPs	Fermentable oligosaccharides, disaccharides, monosaccharides and polyols
SCFAs	Short chain fatty acids
GLUT	Glucose transporter
PGE_2	Prostaglandin E_2
EC cells	Enterochromaffin cells

SIBO	Small intestine bacteria overgrowth
DBPCFC	Double-blind placebo-controlled food challenges
ECRHS III	European Community Respiratory Health Survey III
CI	Confidence interval

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Self-reported food hypersensitivity (SFH) is a common condition among the general population in western societies and a primary cause of functional gastrointestinal (GI) complaints and reduced quality of life (1). Approximately 35% of western inhabitants report intestinal hypersensitivity reactions related to consumption of one or more food items. However, only 1-3% of these incidents are medically diagnosed as IgE-mediated allergic reactions, and more than 90% have irritable bowel syndrome (IBS) (2). This unexplained inconsistency between subjective and medically confirmed food hypersensitivity is frequently observed and a major source of frustration among patients and medical personnel, due to limited diagnostic methods and treatment possibilities. Further investigations are necessary to elucidate the pathological mechanisms of SFH and thus be able to provide proper treatment for these patients. A recent study in atopic patients revealed a strong correlation between elevated serum total immunoglobulin E (IgE) levels and number of mast cells with adherent IgE in duodenal mucosa, thus proposing a potential triggering effect of "IgE-armed" mast cells on the intestinal immune system in SFH patients (3). Additionally, the study also documented an increased intestinal permeability in atopic patients compared to non-atopic patients. The presence of similar histological changes and intestinal dysfunction is also observed in previous studies in patients with atopic diseases, such as dermatitis, eczema, birch pollen allergy, asthma or allergic rhinitis, indicating an association between elevated specific IgE-levels and the GI manifestations observed in patients with functional GI disorders (4-7). Hence, this proposal will focus on whether total IgE levels or atopic sensitization are associated with food-related GI complaints.

This master thesis is developed in compliance with the interdisciplinary MAI team ("Matallergi og Intoleranse", Norwegian translation for food allergy and intolerance) dedicated to the investigation of adult patients presented with GI complaints self-attributed to food hypersensitivity. This team was established at Haukeland University Hospital (HUH) in 2001 and consists of specialist doctors in allergology, gastroenterology and psychiatry, as well as dietician, psychologist, nurses and research fellows. After 2011, the team investigation program was modified.

1.1 Food hypersensitivity

Food hypersensitivity is highly prevalent in the Western population. It is a general term commonly used to describe a person's abnormal reactions to food. The most frequently food items reported as hypersensitive stimuli are cow's milk, wheat, fruits, vegetable, hen's egg, peanuts and seafood (8). The symptoms typically affect the GI tract, but other organ systems can also be involved. According to the last position paper by the European Academy of Allergology and Clinical Immunology (EAACI), the term of food hypersensitivity is used as an overarching term to cover all kinds of adverse reactions to food (9). Food hypersensitivity reactions can be categorized into allergic and non-allergic hypersensitivity reactions as illustrated in figure 1.
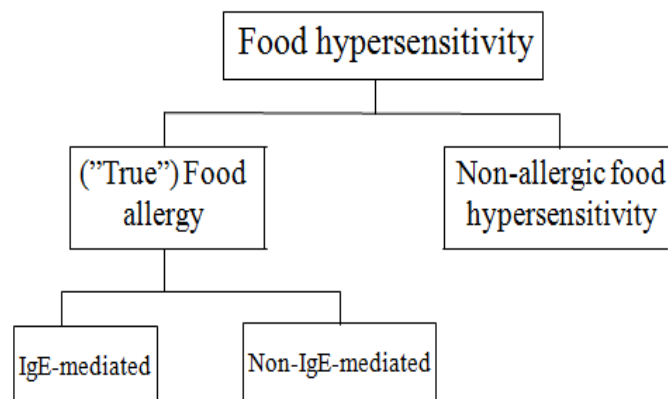
Figure 1: Food hypersensitivity nomenclature. Illustration by Gülen Arslan Lied.

1.1.1 IgE-mediated food allergy

IgE-mediated allergic reactions involve an immediate type I reaction, with mast cell degranulation when these are exposed to antigens attached to antibodies (usually IgE) and subsequent production and release of inflammation mediators like histamine, tryptase and eosinophil cationic protein (ECP) from sensitized immune effector cells, i.e. degranulated mast cells, basophils and eosinophils (10-12). Symptoms occur between a couple of minutes and two hours. The released mediators initiate a rapid immunological response which can cause a variety

of allergic responses, including GI symptoms. Immediate GI hypersensitivity, oral allergy syndrome, acute urticaria, angioedema, acute bronchospasm and allergic rhinitis are the main food allergic disorders, which occur by IgE-mediated mechanisms. The most common allergy symptoms related to the GI tract are abdominal pain, nausea, vomiting, diarrhea and abdominal distention (13, 14).

1.1.2 Non-IgE mediated food allergy

Non-IgE mediated allergic responses involve a much slower cell-mediated reaction, type III or IV, and are usually more difficult to diagnose (15). Reactions can occur within two to 48 hours (late phase reactions), and the initiated immune reactions occur in the absence of IgE. Hence, immunologically sensitized lymphocytes may play a major role. Non-IgE mediated food allergy comprises abnormal reactions in gut generating diverse GI symptoms caused by immunologic responses to contributory food proteins (16). Celiac disease, dietary protein (food-induced) proctitis, enterocolitis and enteropathy are some of the examples of GI diseases related with non-IgE-mediated food allergy (16).

1.1.3 Non-allergic food hypersensitivity

Non-allergic food hypersensitivity comprises much more heterogeneous mechanisms, such as enzyme deficiency (lactose intolerance) or malabsorption in gut, resulting in GI dysfunction and often diverse extra-intestinal symptoms. The state is complex and difficult to diagnose, and comprehensive diagnostic methods are occasionally used to identify the problems (11, 17). Patients reporting non-allergic food hypersensitive reactions are often difficult to diagnose due to their subjective complaints and the presence of functional symptoms that are difficult to objectively measure. Not being able to give an accurate diagnose causes great frustration among these patients, who often feel that they are being neglected by health professionals, given that they do not have a "true" food allergy (15). The situation also results in aggravation for the physicians and other health care personnel who are not capable of provide effective treatment for these patients.

1.1.4 Irritable bowel syndrome

Patients with SFH often have symptoms analogous to IBS complaints and more than 90 % of them are diagnosed as IBS after examination (figure 2) (1, 15, 18). IBS is a functional GI disorder that causes a whole range of various symptoms, whereas abdominal pain and discomfort, bloating and altered bowel habits lasting more than 6 months are the main symptoms triad for IBS. The diagnosis is based on exclusion of any organic causes of GI symptoms and fulfilling the criteria of Rome III consensus. There are no acknowledged biochemical assays or clinical measurements to aid diagnosis. The outbreak of IBS symptoms tends to decrease with aging, and there are more women than men reporting IBS. People suffering from IBS often report that the condition prevents them from everyday life and contributes to reduced quality of life. On average, those affected by the condition absent from work up to 17 days per year, corresponding almost the same absence caused by colds (15, 19). Also, amongst patients who are highly affected by the symptomatic aspects, some may quit their jobs due to impaired quality of life and severe depression (1).
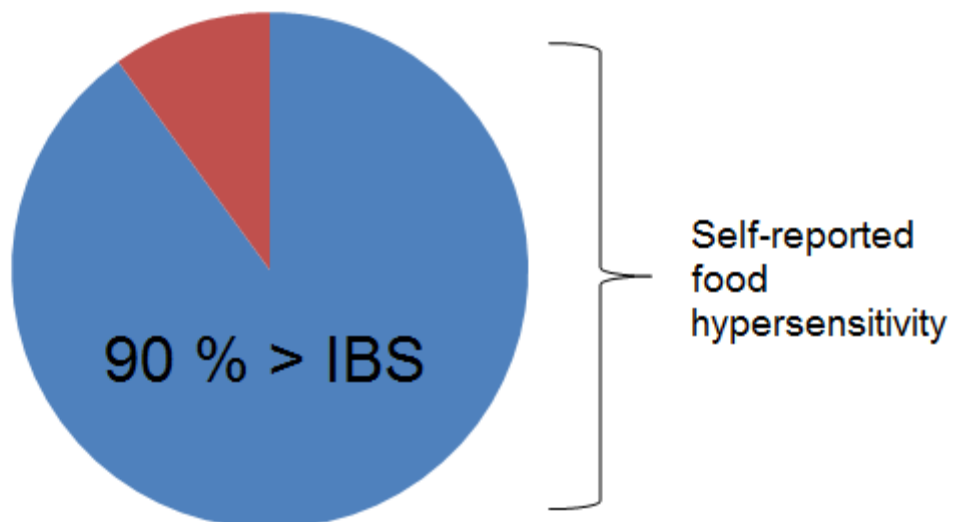
Figure 2: More than 90 % of patients with self-reported food hypersensitivity are diagnosed with IBS after examination. Illustration by author.

1.2 Symptoms

Food-related GI complaints are extensive and often nonspecific. The symptoms are not uniform and can occur in different degrees and at different time periods. Alternating bowel habits, often with diarrhea as predominant, abdominal pain or discomfort, cramps, flatulence and bloating are the most common complaints, which are also consistent with IBS symptoms. It is commonly observed in these patients that discomfort is less prominent in the morning, but exacerbates during daytime. Many experience symptom relief after defecation and frequent bowel movements several times during the day are not uncommon (1, 15, 18). However, feces at night occur rarely in patients with functional GI complaints unlike patients with inflammatory bowel disease, such as Crohn`s disease or ulcerative colitis.

Many patients with SFH find themselves producing extra amounts of intestinal gas, beyond the usual. However, further research has shown that these patients do not necessarily always produce more intestinal gas than healthy subjects, but they are much more sensitive to the excess air formed. This sort of gut hyperalgesia due to gaseous distention is highly recognized in patients with IBS, and is a major key factor contributing to GI complaints. These patients often experience intestinal gas retention and difficulty getting air out (20-22). There may be several explanations for this, whereas emotional problems and stress are the most prominent. Chronic or acute stress may alter gut motility and cause muscle tension, which makes it difficult to relax in bowel. Nevertheless, whilst abundant amounts of gas are the genuine issue, it is conceivable that the problematic air might be related to excessive bacterial fermentation in colon. Patients with functional GI disorders have an abnormal composition of the bacterial flora, and a change in the micro flora has been shown to affect intestine motility and increase the amount of gas produced (20, 21, 23).

The condition also affects other organ systems than the gut. Typical SFH patients also encompass extra-intestinal health complaints, and Lind et al. demonstrated in 2005 a clear association between subjective health complaints and SFH. The incidence of systemic symptoms, such as muscle and joint pains, and the prevalence of anxiety and depression are often high among SFH patients (24). In addition, Berstad and colleagues reported that patients with perceived food hypersensitivity often suffer from chronic fatigue and fibromyalgia, in which they described as food-induced triad. These conditions are often persistent and at least as serious as the digestion-related issues (20, 24, 25). Many of the patients with SFH and IBS also

experience milder forms of dyspepsia and reflux symptoms such as heartburn and acid regurgitate.

Most patients with SFH determinedly believe they react to one or more food items, even though blood tests and skin prick tests are normal. Thus, selected food items are often avoided or totally excluded in diet. Many patients are worried and anxious about which food they can and cannot eat, and due to indiscriminate food avoidance many patients suffering from SFH are often under- or malnourished (17). In addition, anxiety might activate complex neurological networks resulting in cognitive emotional sensitization, which contributes to excessive preoccupation of food and food-related pain and complaints. Above a certain threshold level, the activation of these networks might lead to greater perception of symptoms (24). The patients thus deceive themselves and believe that they react to selected food items even though in reality they do not. Gluten and dairy products are food items frequently reported as symptom triggers and also the products SFH patients typically avoid the most. Hence, these patients are at risk of not getting proper and adequate nourishment (11).

1.3 Pathophysiology

The pathophysiology of SFH is complex and not well understood. Several features have been proposed as potential triggers and the etiology is recognized as multi-factorial (figure 3).
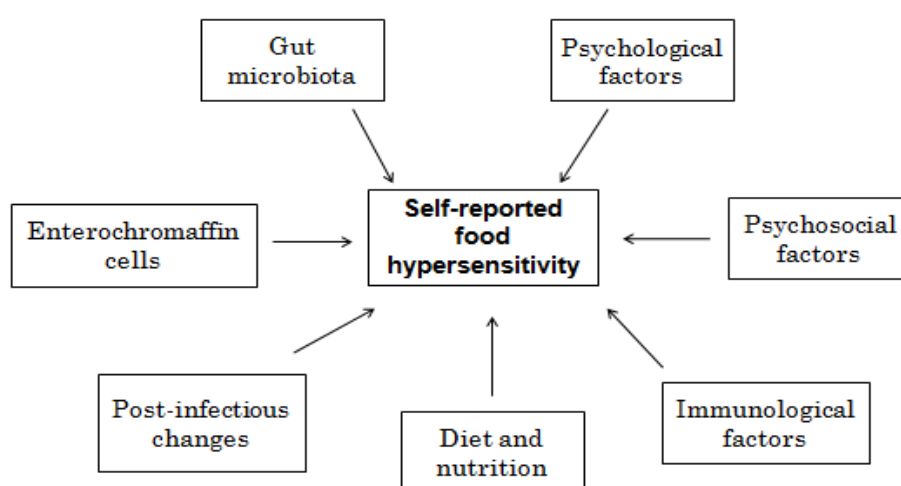
Figure 3: Pathophysiology of self-reported food hypersensitivity. Illustration by author.

1.3.1 Role of psychological and psychosocial factors

The link between the GI tract and the central nervous system (CNS) is highly recognized, and GI disorders are often associated with psychological explanations. Countless of signaling network systems must cooperate in order to have an optimal functioning of gut physiology, and digestive tribulations in the GI tract are often linked to psychological disturbances, but no specific mechanisms have yet been elucidated. However, stress and psychological disorders, such as depression, anxiety and panic disorders, are generally assumed to worsen GI complaints (26, 27). The most common mental disorders among patients reporting SFH are depression and anxiety, whereas anxiety is predominant (28). In addition, reduced quality of life has been shown in these patients due to the unexplained symptoms that affect them in their daily lives and make them incapable of function optimally. However, a study from MAI team performed by Lind and colleagues at HUH, Bergen, indicated that physiological mechanisms could explain only 10 % of the variance in somatic symptoms, indicating that psychological aspects are not as relevant as previously assumed (29). Nevertheless, many patients reporting GI complaints experience that their bowel disorders are perceived as psychosomatic illnesses and these are often referred to psychological therapy in attempt to treat their symptoms. However, a meta-analysis concluded that the effect of carrying out psychological treatment in patients reporting GI complaints had questionable sustainability (24, 30). Also, the efficacy of providing drug therapies such as antidepressant medication for IBS patients has proven to be weak with indistinct evidences. However, anxiety and depression might activate complex networks in the CNS, resulting in cognitive-emotional sensitization and greater awareness of GI symptoms. This could be a major contributor in the development of abdominal hypersensitivity (24, 31, 32). Psychological and environmental factors typical of modern lifestyle, such as stress, health worries and anxiety are suggested as plausible causes of hypersensitivity reactions and have been associated with subjective health complaints. It is anticipated that psychosocial conditions are associated with functional GI diseases, but it is uncertain to what extent (15, 19, 29, 30). A study by Lind et al. in 2005 revealed no significant difference in health worries between patients reporting subjective health complaints and controls. However, patients reported significantly more subjective health complaints than controls, and it is assumed the lack of managing stress and modern lifestyle greatly influences the daily life and contributes to a reduced quality of life in these patients (24).

1.3.2 Role of immunological factors

It is highly recognized that the intestinal immune system closely interact with the enteric nervous system and previous studies from MAI team indicated that local, systemic and mucosal immune systems are activated in patients with SFH. Examples of immunologic biomarkers contributing to GI symptoms and inflammation are histamine, tryptase, calprotectin and ECP. These were measured in gut lavage fluid in a study by Arslan et al. from 2004, where they found that ECP and histamine concentrations were elevated in patients with SFH (18). Despite lack of specific food IgE antibodies, the study suggested that levels of local IgE located in the intestine might contribute to GI complaints (3).

Immune activation is often prominent in IBS patients, and previous studies have suggested an important role of T and B cells in the pathophysiology of IBS. T and B cells are antigen-specific lymphocytes with distinct immunologic functions, upon activating result in an inflammatory immunologic response. In order to activate these cells they must interact with antigen presenting cells (APCs), whereas dendritic cells (DCs) are the most potent APCs. In an attempt to elucidate potential links between accumulations of DCs and SFH, Lied and colleagues performed a study in 2011 where they analyzed DC populations in patients with food hypersensitivity and in controls. No significant difference was observed between DC populations, however atopic participants produced significantly more IL-10, synthesized by monocyte-derived DCs (33). Also, levels of CD38, an immune cell-adherent glycoprotein, proved to be significantly correlated with levels of serum total IgE.

Another study from MAI team at HUH, Bergen, indicated an involvement of B-cell activating factor (BAFF) in non-IgE mediated food hypersensitivity reactions. BAFF is an important regulator of B cell survival and a suggested link in food-related inflammation reactions. In this study, non-atopic patients had significantly higher levels of BAFF in serum and gut lavage fluid than atopic patients. In addition, no significant correlation was observed between BAFF and total IgE, which indicated that BAFF could be an important contributor in non-IgE-mediated allergic reactions to food (34). Recently, a study from Piuri et al. has supported the finding that BAFF is involved in non-IgE mediated allergic reactions. The second pathway of severe allergic reactions required a platelet activating factor (PAF), but not histamine, serotonin or leukotriens, and they found highly significant correlation between BAFF and PAF in non-atopic patients, from which they conclude that BAFF is probably one of the cornerstones of the alternative pathway of

allergy. Hence, the findings regarding increased number of "IgE-armed" mast cells (as mentioned before), BAFF and DCs support the notion of intestinal immune activation in these patients.

1.3.3 Role of nutrition and intestinal fermentation

IBS symptoms associated with GI dysfunction and food hypersensitivity may be triggered or aggravated by selected dietary components and treatment options often involve dietary intervention (35, 36). Many patients experience symptoms postprandial and therefore self-attribute their complaints to specific food items. Low-digestible carbohydrates (LDCs) are poorly tolerated by patients suffering from IBS and SFH, and consumption of LDCs is often reported to replicate symptoms (15, 37). LDCs represent poorly absorbable carbohydrates which are totally or partly fermented in colon, and the term comprises complex carbohydrates (i.e. fiber and starch) and a group of dietary short chained carbohydrates referred to as FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) by Gibson and Shepherd. The group of FODMAPs includes fructose, lactose, fructo- and galactooligosaccharides (fructans, and galactans), and polyols (sugar alcohols: sorbitol, mannitol, xylitol and maltitol). These are poorly absorbable carbohydrates with the capability of water retention due to their osmotic activity, and therefore partially responsible for luminal distention in small intestine and diarrhea. From the small intestine, the LDCs enter colon and accumulation of carbohydrates in colon is problematic in terms of the colonic micro flora. Colonic anaerobic bacteria are capable of fermenting undigested carbohydrates entering colon, yielding methane, hydrogen gas and short chain fatty acids (SCFAs) as fermentation products (figure 4). Excessive bacteria fermentation causes a great deal of problems in hypersensitive patients reporting GI complaints, as a result of colon distention and bloating due to the excess amount of gas produced (15, 35). Thus, dietary LDCs responsible for intestinal water retention and gas production in colon should be avoided in attempt to treat bothersome symptoms such as diarrhea, bloating and flatulence in patients with SFH and IBS. Therefore, consumption of insoluble fibers may worsen GI symptoms and a daily intake of large amounts of dietary fiber is not recommended in patients with IBS complaints, even though dietary fiber and starch in general is recommended to improve health status in the general population. However, in patients experiencing constipation as predominant, an increased intake of fiber is suggested to improve the condition (15, 35, 36).
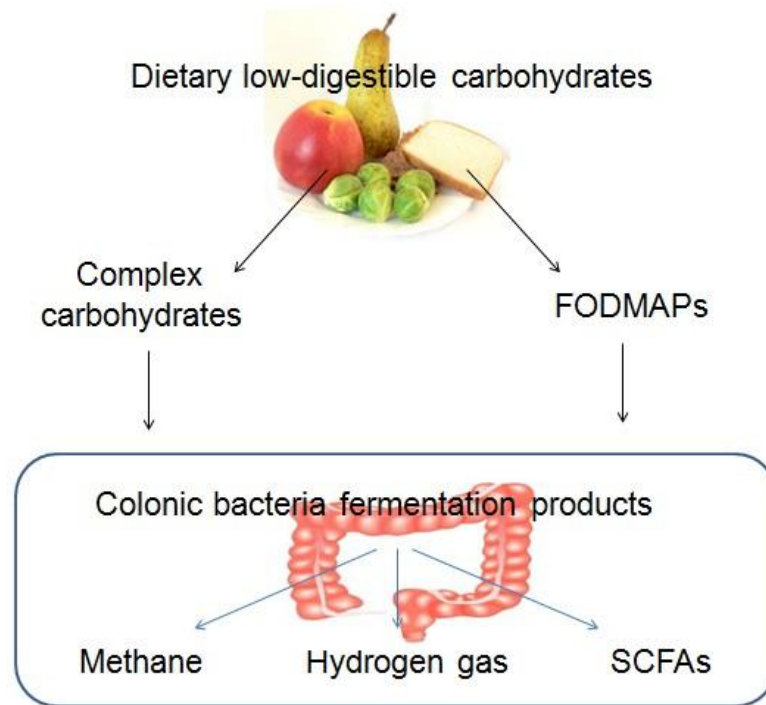
Figure 4: LDCs digestion overview. Illustration by author, edited from www.healthassist.net and www.buzzle.com.

Fructose malabsorption is suggested as an important link in understanding the pathophysiology of food hypersensitivity and food intolerance (38). Fructose is a monosaccharide which is absorbed via two mechanisms in small intestine. When present with glucose, fructose gets efficiently co-absorbed via glucose transporter 2 (GLUT2), whereas when existing in free form fructose is transported via GLUT5, a facultative fructose transporter of low capacity. Therefore, when free fructose is consumed in excessive amounts, the ability to absorb fructose varies, and malabsorption of fructose is common in hypersensitive patients. Thus, unabsorbed fructose remains in intestine lumen and reduces intestinal water flux. The colonic bacteria are capable of metabolizing the fructose load entering colon from the small intestine and generate large amount of gas. Thus, many patients experience symptom relief after fructose avoidance. However, fructose restriction in diet is challenging due to the high content in a variety of consumers food (35). Fructose exists in food as free fructose, sucrose or fructans, which is a fructose polymer. Free fructose is found in many fruits and also honey and syrups. Dietary sucrose is a disaccharide consisting of fructose and glucose, and is not acknowledged as a problem due to the efficient co-transport of the disaccharide via GLUT2. Fructans are found in wheat products and

therefore, many patients who encompass food hypersensitivity symptoms, sometimes experience symptom relief after trying a gluten free diet for a short period.

Administration of omega 3 fatty acids has proven to benefit patients with GI symptoms and joint complaints, and the effect is suggested to be anti-inflammatory. In a pilot study performed by Gregersen and colleagues at HUH, Bergen, duodenal administration of seal oil was implemented in patients reporting food hypersensitivity. It was hypothesized that seal oil possessed the capability to block inflammatory prostaglandin E_2 (PGE_2) synthesis, and therefore inhibit inflammation symptoms. Significant symptom relief was accomplished, indicating a therapeutic effect of seal oil in these patients. However, oral administration had no effect, hence further investigations need to be carried out in this specific area (39).

1.3.4 Role of post infectious changes

Functional GI disorders may also be triggered by other factors, such as intestinal infections (i.e. parasites, bacteria) or frequently use of antibiotics. These factors might disturb the intestinal microbiota, leading to increased permeability, visceral hypersensitivity, low grade inflammation, immune activation among others, and thus initiate IBS manifestations in susceptible individuals (7, 40). A study at the University of Bergen confirmed a 80,5% prevalence of IBS among patients 12-30 months after the onset of a *Giardia lamblia* infection, proposing GI infections as important triggers of functional GI disorders (41).

1.3.5 Role of enterochromaffin cells

Serotonin is an important signaling substance and considered as one of the key neurotransmitters of the enteric nervous system prevalent in the gut. Generally, 95 % of the body's content of serotonin is believed to remain in the gut system. The substance is synthesized and secreted by the enterochromaffin (EC) cells, a subtype of enteroendocrine cells present in small intestine. Serotonin is released by these cells through luminal stimuli, and it is involved in a numerous gut functions, including GI motility, reflex coordination, secretion and sensation. Abnormal luminal contents of serotonin and alterations in serotonin metabolism may initiate GI symptoms and have been implicated in GI disorders including IBS and food hypersensitivity. As such, serotonin is suggested as an important biomarker in the pathophysiology of SFH (42, 43). However, a study

by Gregersen et al. from 2011 revealed no significant differences in levels of 5-hydroxytryptamine (5-TH, serotonin) in gut lavage fluid between patients with subjective food hypersensitivity and controls (44).

1.3.6 Role of gut microbiota

Recently, there has been an increased interest in the role of gut bacteria in functional GI disorders, and small intestine bacteria overgrowth (SIBO) has been suggested as a potential pathophysiological mechanism. SIBO indicates an abnormal escalation of the bacteria flora colonizing the small intestine, in which induce symptoms similar to IBS complaints. A high prevalence of SIBO in IBS patients is observed, and the condition is diagnosed by performing a lactulose breath test, in which increased amounts of gas in exhaled air indicates SIBO. Also, antibiotics and SIBO eradication has proven to improve symptoms in IBS patients (45, 46).

In addition, recent investigations conclude that many symptoms associated with GI dysfunction can be explained due to dysbiosis of the gut micro flora. As mentioned, the bacteria colonizing the large intestine are important due to decomposition of indigestible food components entering the colon, and in maintaining a healthy bowel. An abnormal SCFA composition and excess amounts of gas is observed in many patients with GI complaints, indicating an unbalanced bacteria flora and disrupted fermentation process in these patients. These findings may in future be clinical applicable in elucidating important links in the pathophysiology of functional GI diseases (35, 47).

The therapeutic effect of applying live microorganisms denoted as probiotics have been widely investigated and the appreciation of its health benefits in relation to IBS patients is growing. It is suggested that administration of multi-species probiotics may benefit the intestinal micro flora and reduce GI symptoms severity due to microbiota imbalance (36, 48). Additionally, fecal bacteriotherapy has been widely used as treatment for chronic GI infections, with successful results. Bacteriotherapy includes transplantation of the intestinal fecal flora from a healthy donor into a recipient, and optimistic results have also been observed in patients with IBS after administration (49). However, this kind of treatment needs further investigations and additional follow up-studies.

1.4 Diagnostic challenges

Patients reporting functional GI complaints self-attributed to specific food items are at first referred by their physician to undergo allergologic examinations. These investigations include identifying the patients full medical history, skin prick tests and measurement of allergy parameters in serum, including specific IgE levels against susceptible food allergens (50). Also, elimination diets, open food challenges and double-blind placebo-controlled food challenges (DBPCFC) are often performed by dietitians to further investigate the patients' different reactions to selected food. DBPCFC is highly recognized and is designated as the gold standard of identifying food allergy. Nevertheless, due to diffuse and subjective symptoms in patients reporting non-allergic food hypersensitivity, there are no validated diagnostic methods to verify the various complaints, thus patients are often diagnosed IBS when other organic diseases are excluded. Diagnosing IBS in patients with food hypersensitivity is based on addressing the Rome III criteria. However, this criteria does not reflect the patients overall complaints and health issues, such as fibromyalgi and fatigue, which often are dominant symptoms among SFH and IBS patients (51). As such, the patients do not obtain an exact diagnose and they remain uncertain about their condition, not knowing what to do in attempt to improve their health status.

Scientists and physicians wish to come up with improved diagnostic methods for non-allergic food hypersensitivity, whereas intestinal allergen provocation test with endosonography and two-dimensional external abdominal ultrasound are examples of potential future techniques which could help physicians in obtaining more accurate diagnoses. During these tests, changing in intestinal wall thickness, peristaltic activity and luminal fluid could be monitored after administration of food allergen directly into the duodenum by a nasogastric sonde. However, these are preliminary research tools and must be validated before further use. Analyses of inflammatory immunologic markers, such as tryptase or ECP in serum, urine or gut lavage fluid, are also suggested as diagnostic tools for identifying patients reporting food hypersensitivity (11, 52).

Increased luminal levels of serotonin in intestine have, as previously mentioned, been proposed as an indicator of gut dysfunction in SFH patients. Biopsies and subsequent immunoassay determination are proposed methods for determining serotonin status in patients. Also, Gregersen et al. developed in 2007 a new method to measure serotonin level in gut lavage fluid in attempt to evaluate the serotonin status in SFH patients (42). However, the effect of serotonin and EC cells on the pathophysiology of GI disorders remains unclear.

The role of brain-gut axis dysregulation is not entirely confirmed, however the modularity effect of the CNS in gut motility and pain perception is highly recognized. In the last decades a remarkable development in brain imaging techniques has followed in an attempt to legitimize patients reporting undiagnosed functional GI symptoms. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and also molecular examination of neurologic peptides are new procedures proposed to detect abnormalities in the brain-gut axis. These methods make it potentially possible to study the physiology of the brain and possibly understand the intrinsic role of CNS in modulating pain and motility in the gut (50, 53).

1.5 Total IgE and atopic sensitization

In a study at HUH, Bergen, from 2010, Lillestøl and colleagues discovered a significant correlation between elevated levels of serum total IgE and increased number of mast cells in duodenal mucosa in atopic patients, mainly as "IgE-armed" mast cells. Mast cell stimulation upon allergen exposure initiates degranulation and subsequent release of various mediators (figure 5).
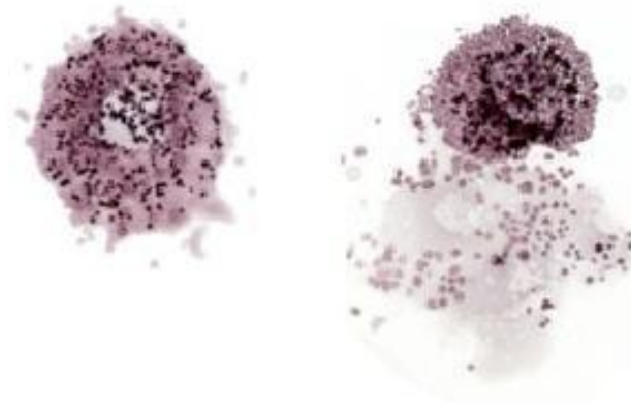
Figure 5: Mast cell degranulation. Illustration by www.brycelab.com.

These mediators, including histamine and tryptase, were hypothesized by Barbara et al. to have the capability of altering the physiology of the enteric nervous system and lead to visceral hypersensitivity. In their study from 2004 they demonstrated a significant correlation between

abdominal pain and the presence of degranulated mast cells in IBS patients. Also, they detected an increased density of mast cells in proximity to nerves supplying the colonic mucosal (3, 53). In addition, mast cell release of other pro-inflammatory mediators can result in inflammation and cause a number of symptoms affecting the GI tract. It was thus suggested that "IgE-armed" mast cells might represent a pathological explanation due to subjective GI complaints in patients with functional GI disorders.

Previous studies in children and adolescents with asthma revealed a relationship between higher levels of total serum IgE and impaired pulmonary function (reduced FEV1/FVC) (54-56). Haselkorn et al. examined the relationships of age and sex with allergic co-morbidities and total serum IgE levels with airflow in a cohort study, and observed a high rate of allergic rhinitis, atopic dermatitis, and sensitization to allergens (57). Higher levels of serum total IgE were associated with lower pre-bronchodilator FEV1/FVC, independent of age, sex, and race/ethnicity, suggesting that total IgE may be a marker of asthma severity. However, such relationships between total IgE levels and GI complaints have not previously been investigated in patients with food hypersensitivity.

Despite a low prevalence of classical specific IgE-mediated food allergy among patients who self-attribute GI complaints to food hypersensitivity, it is speculated that other atopic disorders (such as rhinitis, eczema and asthma) may play a role in the development of such complaints (18, 28, 58). Patients with atopic background have higher level of specific IgE than non-atopic patients, and additional studies have elucidated that individuals with atopic diseases report more food hypersensitivity reactions than non-atopic (3, 59). This might represent a pathological link between functional GI disorders and increased levels of specific IgE antibodies in atopic patients (25). Elevated levels of specific IgE in blood serum indicate that the atopic patient is sensitized and more susceptible to evolve hypersensitive reactions to specific food items (60). Also, atopic patients with elevated specific IgE to pollen antigens can experience hypersensitization due to potential cross reactions with food antigens capable of conformation intended for IgE-interaction [9]. In a pilot study performed by Tobin and colleagues a strong correlation was observed between patients with atopic manifestations and the presence of IBS symptoms compatible with the Rome II Criteria (7). Consistent with these findings "atopic IBS" was recently proposed as a new subgroup of IBS, possibly with a distinct role of mast cells.

Our aim in this extended study was to explore the relevance of total IgE and atopic sensitization in patients with IBS-like complaints self-attributed to food hypersensitivity. We know from

previous studies on functional GI disorders, that there are differences in gender and age when it comes to reporting GI complaints (20), and it has been documented that women on average report more bowel symptoms and IBS-like complaints than men. Also, GI complaints seem to tender with younger individuals, i.e. elderly appear to experience less GI complaints (20). Therefore, we also wanted to explore the impact of age and gender differences when it comes to the association between levels of total IgE or atopic sensitization and GI complaints.

2. AIMS OF STUDY

Our main objective was to investigate the association between total IgE, atopic sensitization and GI symptoms. The specific aims of this proposal were as follows:

➢ To investigate the association between serum total IgE levels and GI complaints.

➢ To investigate the association between atopic sensitization and GI complaints.

➢ To analyze whether there is a gender difference in the association between total IgE and GI complaints.

➢ To analyze whether there is an age difference in the association between total IgE and GI complaints.

3. MATERIALS AND METHODS

3.1 Patients

A total of 161 patients with or without GI complaints referred by general practitioners to Section of Clinical Allergology, at the Department of Occupational Medicine, HUH for suspected allergy were indiscriminately recruited in our study from February 2011 to September 2013. The patients without GI complaints as primary cause of reference were a comparable group for the patients with GI symptoms. In addition, a group comprising 479 individuals, was provided from the European Community Respiratory Health Survey (ECRHS III) study to represent the general population. Our data were categorized as follows;

A patient group divided in two subgroups according to primary cause of reference, i.e. patients who are referred to allergological examination with GI complaints as primary cause of reference (n=81) and patients who are referred to allergological examination with other allergic symptoms as primary cause of reference (n=80).

A group sample representing the general population (n=479).

All participants went through standard "allergy screening" and completed attached questionnaires. Patients with organic disease which could explain their abdominal symptoms, pregnant or lactating women were excluded.

3.2 Allergological examination

Allergological examination consisted of detailing patient's history including levels of total and food-specific IgE. In the patient group, levels of total and specific IgE were analyzed by ImmunoCap-System (Phadia, Uppsala, Sweden). Inhalant and food allergens were measured using standard panels of Phadiatop (i.e. birch, timothy, *Cladosporum herbarum*, cat, dog, horse, mugwort, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and fx5 food screening (i.e. cow's milk, egg white, wheat flour, soya, cod and peanuts). In the general population provided from ECRHS III, levels of total and specific IgE were analyzed using the Pharmacia CAP System (Pharmacia Diagnostics, Uppsala, Sweden). Specific IgE included *Dermatophagoides pteronyssinus*, cat and timothy.

Participants were divided into atopic and non-atopic subgroups, according to specific IgE levels in serum: Atopic individuals were defined by having increased levels of specific IgE antibodies to at least one allergen (> 0.35 kU/L).

3.3 Questionnaires assessing GI complaints

During the first session, all participants were asked to fill in two questionnaires to assess their GI complaints regarding symptoms and diagnosis of their complaints:

The Questionnaire for Rome III criteria and functional GI complaints included the short form of the Rome III criteria and IBS Symptom Questionnaire, which both are widely used in diagnosing IBS and in quantification of functional GI disorders (61). The IBS symptom questionnaire (IBS-SQ) contains 6 symptoms which are rated on a scale of 0 - 10, where 0 = no symptoms and 10 = severe IBS. A total score of 15 or higher defined active symptoms for patients with IBS. In addition, the questionnaire also included four IBS criteria providing support for IBS diagnosis, four symptoms requiring further consideration, three criteria for functional dyspepsia, two symptoms supporting heartburn diagnosis and four additional questions to characterize all patients.

IBS Symptom Severity Scale (IBS-SSS): The IBS-SSS contains five questions that are rated on a 100-point visual analogue scale (VAS), in which are meant to give information about the severity of abdominal pain, the frequency of abdominal pain, the severity of abdominal distension, dissatisfaction with bowel habits, and the GI complaints' interference with quality of life (62). All five components contribute to the score equally yielding a theoretical range of 0 – 500, with a higher score indicating a worse condition. Previous studies have established that scores below 175 represent mild IBS symptoms, 175–300 represents moderate severity, and scores above 300 represent severe IBS (62). A decrease of 50 points on the IBS-SSS has been shown to correlate with improvement in clinical symptoms.

3.4 European Community Respiratory Health Survey

The European Community Respiratory Health Survey (ECRHS) is a multicentre, international study initially set up in the early 1990's to assess the prevalence of asthma and allergy in young to middle aged adults. Random population samples were selected within administrative boundaries in each study centre. At baseline, about 200,000 men and women answered a screening questionnaire, and approximately 26,000 persons participated in a clinical investigation. A follow-up study of the clinical cohort in 29 study centers, ECRHS II, was carried out in 1998-2002. The data collection of the third wave, the ECRHS III, has recently been performed. The ECRHS has been funded by the European Commission as part of the Quality of Life Programme, as well as by other sources. Over 500 papers have been published.

From Norway, Bergen participates in the ECRHS. At baseline, a random population sample of 4300 persons were invited to a screening questionnaire, and a subsample of 1200 responders were invited to a clinical examination of which 935 subjects took part. Six hundred subjects were re-investigated in 2000-01. In 2011, 12 475 persons have participated in the clinical follow-up, investigated with interview, lung function measurements, blood samples, skin prick tests and self-filled in questionnaires. The participants were asked to fill in two questionnaires about GI complaints (*The Questionnaire for Rome III criteria and functional GI complaints* and *IBS Symptom Severity Scale*). Total and specific IgE were analyzed as described above.

3.5 Categorization of data and statistical analysis

All data for patients were registered in FileMaker Pro 5.5 (Inc, California) by the same person. For participants from the ECRHS III study, the data were collected in IBM SPSS Data Collection Data Entry.

Statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 21, Inc. Chicago. We included two parameters to assess GI complaints severity, i.e. IBS-SSS and IBS-SQ. Pearson's correlation coefficient was used to assess the correlation between parameters including total IgE levels and severity of GI complaints, and the correlation analyzes were bivariate and two-tailed. Independent Student t-tests and one-way Anova were used for comparisons of means in different groups, followed by post hoc Scheffé pairwise comparisons.

Chi-square statistics were used for comparisons of proportions. Linear regression models were used to evaluate the association between total IgE levels and GI complaints (IBS-SSS), adjusting for atopic sensitization, gender, age and sample in multivariate regression models. A statistical value of $p < 0.05$ was considered statistically significant.

3.6 Ethical Approval

The clinical study was approved by the Regional Committee for Medical Research Ethics (REK 2011/1118) and all patients and controls have given written informed consent.

4. RESULTS

4.1 Demographic and clinical characteristics of the study populations

Table 1 presents demographic data and characteristics among patients (referred for GI complaints or for other allergic complaints) and in the general population.

Table 1: Demographic and clinical data in the study populations, a patient group and a general population sample.

	Patient subgroups		Patient group	General population
	With GI complaints	**With other complaints**		
N	81	80	161	478
% Women	72.8 % (n=59)	67.5 % (n=54)	70.2 % (n=113)	44.7 % (n=214)
% Men	27.2 % (n=22)	32.5 % (n=26)	29.8 % (n=48)	55.3 % (n=264)
Age, mean years (range)	36.51 (17-75)	37.29 (15-71)	36.90 (15-75)	52.51 (40-64)
IBS-Symptom Questionnaire (IBS-SQ) (mean)	23.74	13.96	19.05	5.92
IBS-Symptom severity scale (IBS-SSS) (mean)	267.49	116.67	193.07	70.77
IBS-SSS				
>300(severe)	33.3 % (n=27)	7.50 % (n=6)	20.50 % (n=33)	1.88 % (n=9)
175-300 (moderate)	42.0 % (n=34)	22.50 % (n=18)	32.30 % (n=52)	5.65 % (n=27)
75 - 175 (mild)	16.0 % (n=13)	21.25 % (n=17)	18.63 % (n=30)	25.70 % (n=123)
<75 (no IBS)	3.7 % (n=3)	42.5 % (n=34)	22.98 % (n=37)	62.34 % (n=298)
Allergy				
Total IgE (mean)	279.79	336.22	312.94	75.5
Total IgE levels >120 kU/L	45.7 % (n=37)	52.5 % (n=42)	49.07 % (n=79)	12.97 % (n=62)
Inhalant allergens positive	55.6 % (n= 45)	80 % (n=64)	67.7 % (n=109)*	21.5 % (n=103)***
Food allergens positive	37.0 % (n=30)	46.3 % (n=37)	41.61 % (n=67)**	
Atopic (%)	56.8 % (n=46)	82.5 % (n=66)	69.57 % (n=112)	21.5% (n=103)

* % with positive specific IgE (< 0.35 kU/L) to at least one inhalant allergen (Standard panels of inhalant, Phadiatop, ImmunoCAP, Phadia AB, Uppsala, Sweden).
** % with positive specific IgE (< 0.35 kU/L) to at least one food allergen (Standard panels of food (fx5) allergens (ImmunoCAP, Phadia AB, Uppsala, Sweden).
*** % with positive specific IgE (< 0.35 kU/L) to one of the following inhalant allergens: grass, cat or *Dermatophagoides pteronyssinus*.

The presence of atopic sensitization and elevated levels of specific IgE and total IgE were higher in both patient subgroups compared to the general population. Timothy and birch were the most common inhalant allergens in patients with GI complaints, whereas sensitization to timothy, *Dermatophagoides pteronyssinus,* birch and dog were most common in patients with other

complaints. With regard to food allergens, hazelnut, wheat and peanut were the most common allergens in patient group (tables are presented in Appendix 5, table 1 and 2).

Both patient subgroups had more GI complaints than the general population (table 2). Among patients, abdominal pain was the most common GI symptom, affecting 123 patients (76.4 %), followed by changes in frequency of stool (59 %) and bloating (61.5 %), which is consistent with IBS triad. In the general population, bloating and diarrhea were the most common symptoms (table 2).

Table 2: Specific GI complaints in the study populations

	Patient group		Patient group	General populatio
	With GI complaints	**With other complaints**	**Patient group**	**General populatio**
% GI complaints				
- % with abdominal pain or discomfort last 3 months	96.3 % (n=78)	56.3 % (n=45)	76.4 % (n=123)	29.0 % (n=139)
- % change in frequency of stool	79.0 % (n=64)	38.8 % (n=31)	59.0 % (n=95)	22.3 % (n=107)
- % with bloating and/or abdominal distention	76.5 % (n=62)	46.3 % (n=37)	61.5 % (n=99)	41.3% (n=198)
- % with defecation at night	19.8 % (n=16)	8.8 % (n=7)	14.3 % (n=23)	2.7 % (n=13)
- % with diarrhea predominant	61.7 % (n=50)	40.0 % (n=32)	50.9 % (n=82)	38.6 % (n=185)
- % with constipation predominant	27.2 % (n=22)	16.3 % (n=13)	21.7 % (n=35)	15.4 % (n=74)
- % med functional dyspepsia	65.4 % (n=53)	23.8 % (n=19)	44.7 % (n=72)	15.9 % (n=76)
- % with heartburn	49.4 % (n=40)	31.3 % (n=25)	40.4 % (n=65)	28.8 % (n=138)

Figure 6 presents an illustration of IBS-SSS scores (A) and IBS-SQ scores (B) in the different groups. Both patient subgroups reported more GI complaints than the general population (p < .001), and this was the same for both scoring systems of GI complaints. Patients with other complaints reported less abdominal complaints than patients with GI complaints (p < .001).
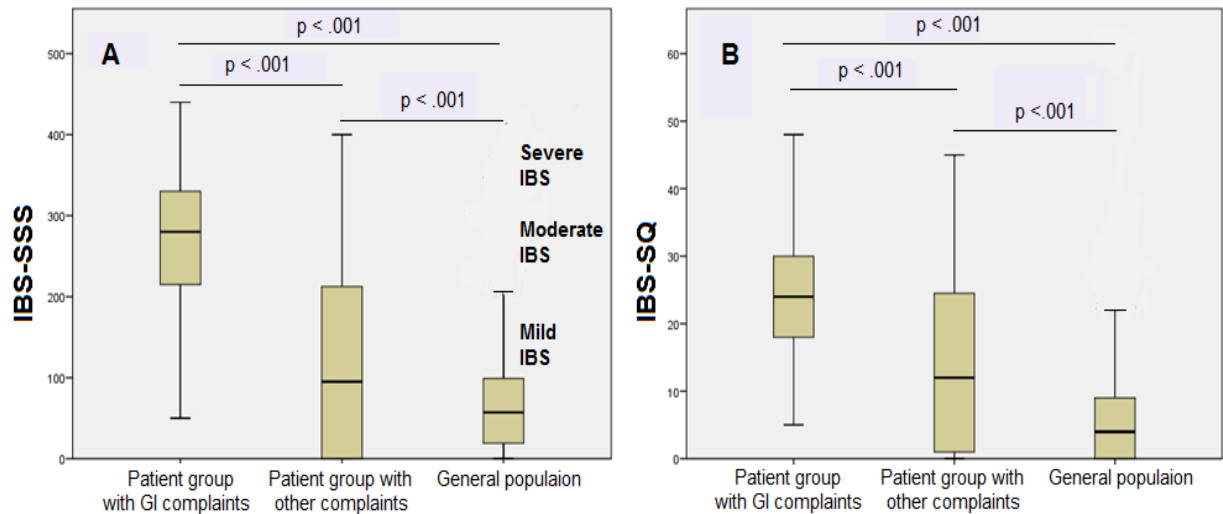
Figure 6: (A) IBS-SSS scores, including IBS grading score, and (B) IBS-SQ scores between different groups, giving us the medians, interquartiles and 95 % confidence intervals.

According to table 1 and figure 7, total IgE levels were higher in patient subgroups compared to the general population (patients with other complaints: mean = 336.22, patient group with GI complaints: mean = 279.78 and general population: mean = 75.7) (p < .001). Within the patient subgroups, patients with other allergic symptoms as cause of reference had higher levels of total IgE compared to patients referred for GI complaints, however this difference was not significant (p = .563).
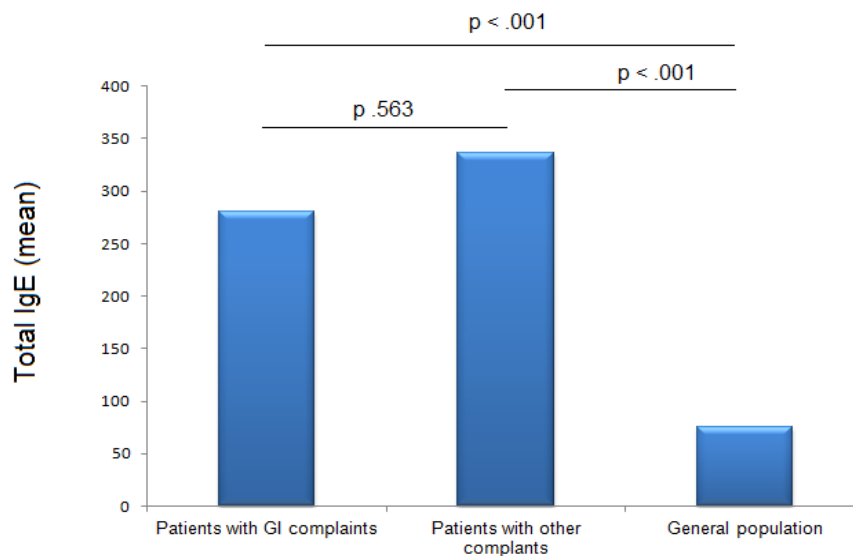
Figure 7: Means of total IgE in the different groups.

The distribution of atopic sensitization did significantly differ between groups (p < .001), whereas the patient subgroup with other complaints had also the highest prevalence of atopic sensitized (figure 8).
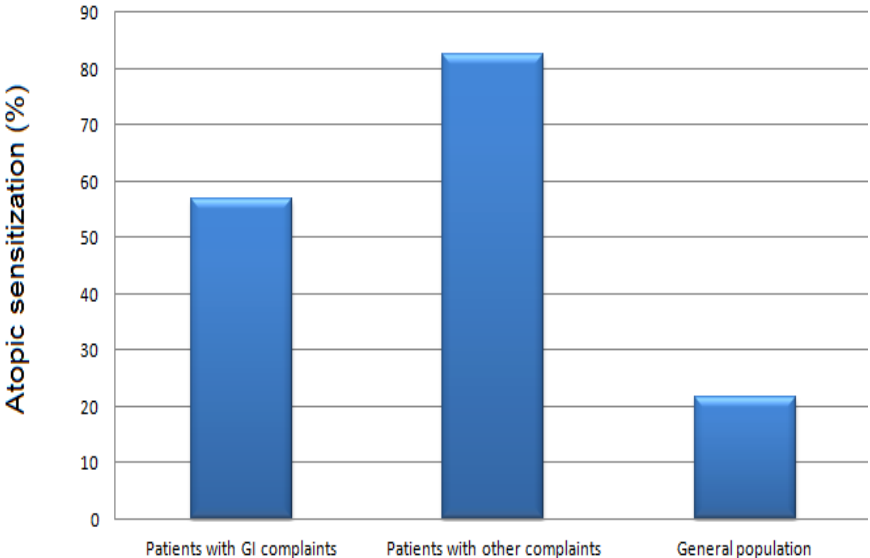
Figure 8: Prevalence of atopic sensitization in the study populations.

4.2 Bivariate relationship between GI complaints and total IgE

We conducted correlation analyzes for the patient group and general population in order to test whether levels of total IgE correlated with GI complaints, i.e. IBS-SSS and IBS-SQ.

Patient group

No significant correlation was observed between total IgE and IBS-SSS (r = .072, p = .379) or total IgE and IBS-SQ (r = .084, p = .311) (figure 9, A and B). Analyzing each patient subgroup separately revealed no significant correlations (Appendix 6, figure I and II).
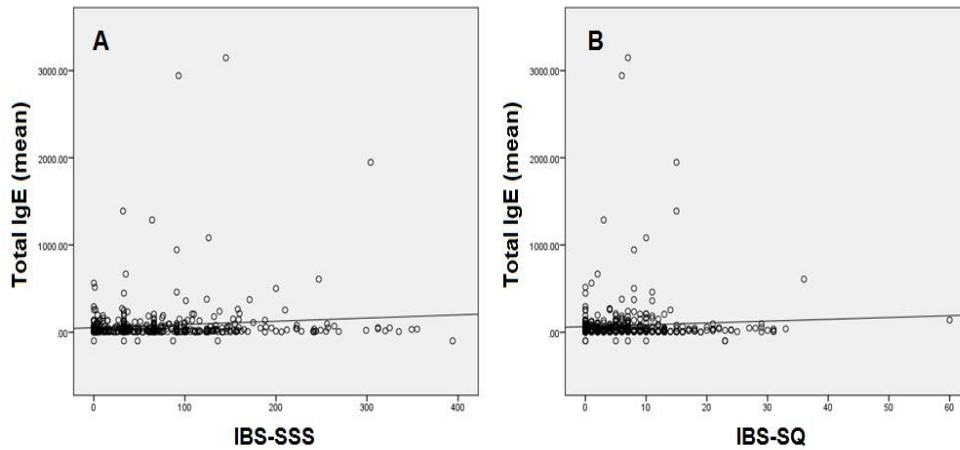
Figure 9: Correlation analyzes in patient group (n = 161) between A: total IgE and IBS-SSS (r = .072, p = .379) and B: total IgE and IBS-SQ (r = .084, p = .311).

General population

In the general population group, a significant correlation was discovered between total IgE and IBS-SSS (r = .102, p = .029), but not between total IgE and IBS-SQ (r = .059, p = .201) (figure 10, A and B).
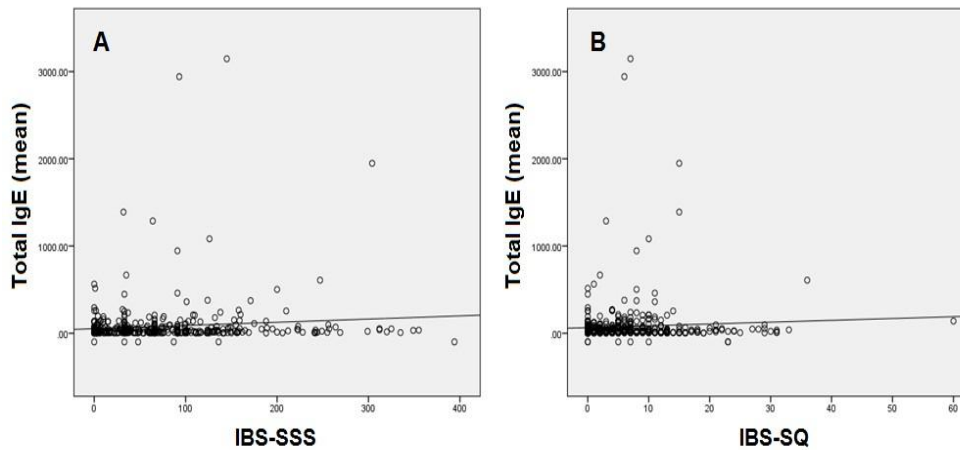
Figure 10: Correlation analyzes in general population between A: total IgE and IBS-SSS (r = .102, p = .029) and B: total IgE and IBS-SQ (r = .059, p = .201).

37

4.3 Bivariate relationship between GI complaints and atopic sensitization

Patient group

We conducted an independent t-test in the patient group in order to compare GI complaints (IBS-SSS scores and IBS-SQ scores) in atopic and non-atopic persons (atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) and/or standard panels of food allergens (fx5) in the patient group).
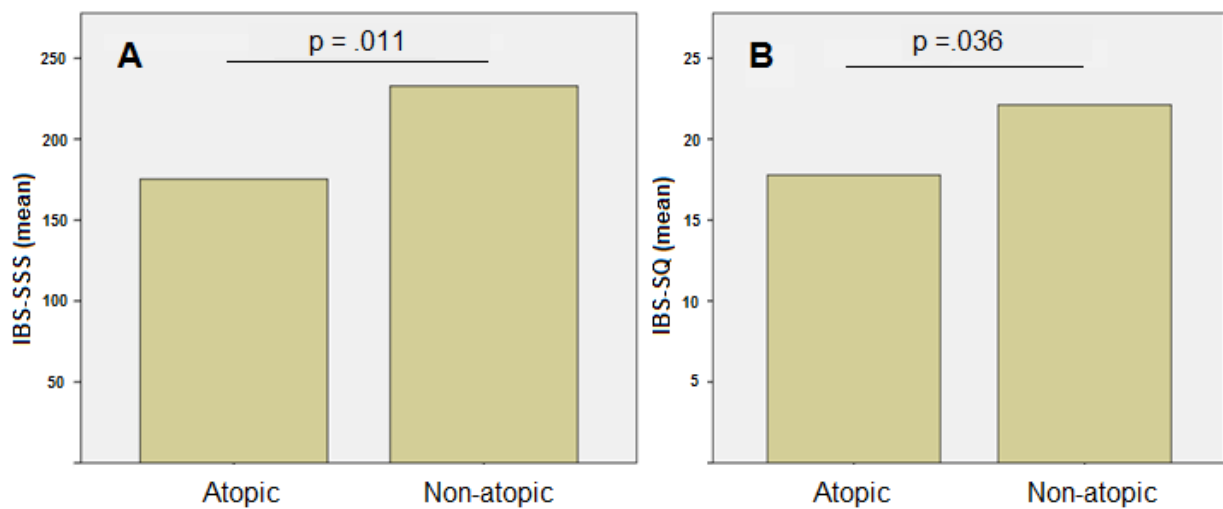
Figure 11: Mean IBS-SSS scores (A) and mean IBS-SQ scores (B) between non-atopic and atopic in patient group.

We observed a significant difference in IBS-SSS scores (p = .011) and IBS-SQ scores (p = .036) between groups (figure 11, A and B). The non-atopic persons reported on average significantly more GI complaints (mean IBS-SSS = 232.77, mean IBS-SQ = 22.11) than atopic persons (mean IBS-SSS = 175.30, mean IBS-SQ = 17.77), and this was consistent for both scoring systems for GI complaints. Independent t-tests comparing means in IBS-SSS and IBS-SQ between atopic and non-atopic in patient subgroups are presented in Appendix 7, figure III and IV.

General population

A similar tendency was observed in the general population sample (figure 12, A and B), and in this study sample atopic sensitization was defined as having elevated levels (> 0.35 kUa / L) of specific IgE to at least one of the following allergens: *Dermatophagoides pteronyssinus*, cat or grass. On average, non-atopic persons reported more GI complaints (mean IBS-SSS = 71.71) than atopic persons (mean IBS-SSS = 64.48). However, this difference was not statistically significant (p = .362). The same results was observed when comparing IBS-SQ means, whereas non-atopic reported more GI complaints (mean IBS-SQ = 6.07) than atopic (mean IBS-SQ = 5.18), but the difference was not significant (p = .268).
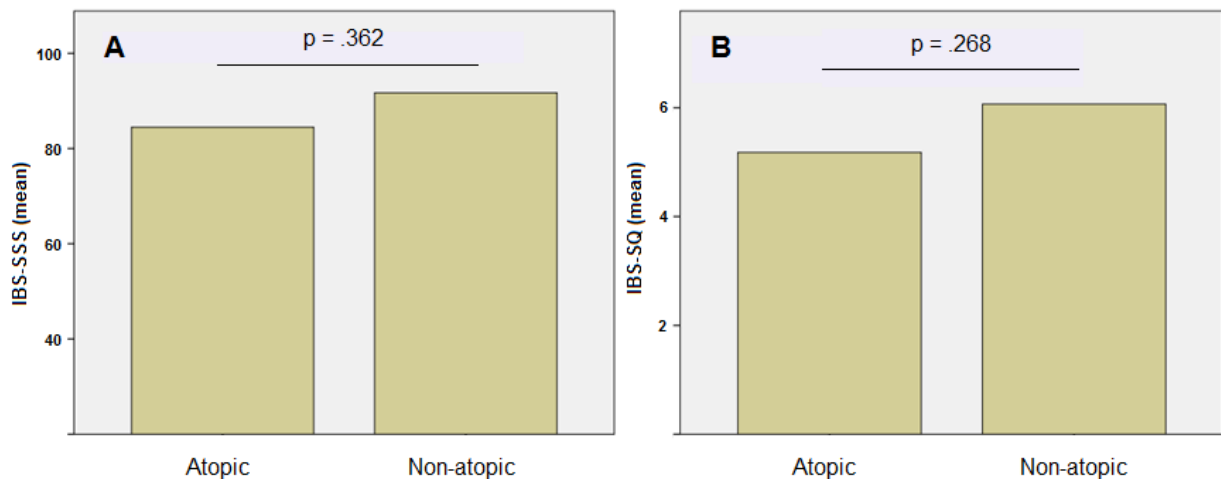
Figure 12: Mean IBS-SSS score (A) and mean IBS-SQ score (B) between non-atopic and atopic in general population.

4.4 Multiple regression analyzes of predictors of GI complaints

We conducted multiple linear regression analyzes in order to investigate the association between total IgE, atopic sensitization, sex, age and GI complaints (IBS-SSS) in the patient group and in the general population.

In the following statistical analyzes we have only implemented IBS-SSS scores as a marker of GI complaints, because IBS-SSS and IBS-SQ were highly correlated in both patient group (r = .798, p < .001) and in the general population (r = .664, p < .001), indicating similar findings in relation to atopic sensitization and total IgE as shown below (regression analyzes including IBS-

SQ are presented in Appendix 8, table III - V). The regression models are considered as robust, given that the coefficients do not change front signs and have no dramatically different values in the second model with statistical adjustments. All changes in Δ-values in the regression and interaction analyzes are calculated as new value minus old value, and levels of confidence intervals (CI) are set at 95% for all unstandardized regression coefficients.

Patient group

Table 3: The association between GI complaints (IBS-SSS) and total IgE, atopic sensitization, sex and age in patient group, analyzed with multiple regression analysis. Model 1 is unadjusted and model 2 is adjusted for atopic sensitization, sex and age.

	IBS-SSS			
	B	95 % CI	SE b	p-value
Model 1 (unadjusted)				
Total IgE	.019	(-.023, .061)	.021	.379
Model 2				
Total IgE	.036	(-.007, .078)	.021	.097
Atopic sensitization*	-77.216	(-124.292, -30.140)	23.818	**.001**
Sex	-1.048	(- 45.676, 43.580)	22.580	.963
Age	-1.338	(-2.717, .042)	.698	.057

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .005 for model 1, ΔR^2 = .080 for model 2 (p = .012).
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) and/or standard panels of food allergens (fx5).

Total IgE was positively associated with GI complaints, however the association was not significant (b = .019, p = .379) (table 3, model 1). When adjusting for sex, age and atopic sensitization (model 2), the association between total IgE and GI complaints was borderline significant (b = .036, p = .097). Measured by the p-values, atopic sensitization was the largest contributor, which was significantly associated with less GI complaints (b = -77.216, p = .001). Total IgE accounted for 0.5 % of the total variance in GI complaints in the unadjusted analysis of the patient group. When sex, age and atopic sensitization were included in the multiple regression model, the amount of explained variance increased to 8.0 % (p = .012). Total IgE and atopic sensitization could together explain 6.2 % of total variance in GI complaints in a multiple

regression model only adjusting for levels of total IgE and atopic sensitization ($\Delta R^2 = .062$, p = .009).

General population

Table 4: The association between GI complaints (IBS-SSS) and total IgE, atopic sensitization, sex and age in the general population, analyzed with multiple regression analysis. Model 1 is unadjusted and model 2 is adjusted for atopic sensitization, sex and age.

	IBS-SSS			
	b	95 % CI	SE b	p-value
Model 1 (unadjusted)				
Total IgE	.028	(.003, .054)	.013	**.029**
Model 2				
Total IgE	.038	(.012, .064)	.013	**.005**
Atopic sensitization*	-14.394	(-30.670, 1.883)	8.282	.083
Sex	-8.980	(-21.939, 3.979)	6.594	.174
Age	-.360	(-1.327, .607)	.492	.464

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .010 for model 1, ΔR^2 = .014 for model 2 (p =.027).
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to one of the following allergens: grass, cat or *Dermatophagoides pteronyssinus*.

In the general population sample, total IgE was significantly associated with IBS-SSS in both the unadjusted analysis and the adjusted analysis (table 4). The size of the estimate was similar as to that in the patient group (b = .038, p = .005 and b = .036, p = .097, respectively). A negative association with atopic sensitization was detected in the general population (b = -14.394, p = .083) (table 4, model 2), as also seen in the patient group. Total IgE accounted for 1.0 % of the total variance in GI complaints in unadjusted analysis of the general population sample. Total IgE and atopic sensitization could together explain 1.9 % of total variance in GI complaints in a multiple regression model only adjusting for levels of total IgE and atopic sensitization ($\Delta R^2 =$ .019, p = .014).

Total study population

Because similar associations were detected among patients and in the general population, these groups were merged into one group in order to obtain a larger sample. Notable modifications in the adjusted regression model were definition of atopic sensitization and the introduction of a group sample variable.

Table 5: The association between GI complaints (IBS-SSS) and total IgE, atopic sensitization, sex, age and sample in total study population (n = 639), analyzed with multiple regression analysis. Model 1 is unadjusted and model 2 is adjusted for atopic sensitization, sex, age and sample.

	IBS-SSS			
	b	95% CI	SE b	p-value
Model 1				
Total IgE	.065	(.041, .088)	.012	**<.001**
Model 2				
Total IgE	.037	(.015, .059)	.011	**.001**
Atopic sensitization*	-33.855	(-50.963, -16.748)	8.711	**<.001**
Sex	-7.471	(-21.810, 6.869)	7.301	.307
Age	-.788	(-1.530, -.046)	.378	**.037**
Patient group or general population group	115.888	(94.601, 137.175)	10.839	**<.001**

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .046 for model 1, ΔR^2 = .251 for model 2 (p < .001).
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) in patient group and as having elevated specific IgE (> 0.35kU/L) to grass, cat or *Dermatophagoides pteronyssinus* in general population.

Due to the lack of data on specific IgE to food allergens and selected inhalant allergens in the general population, we excluded data on food allergens in the patient group, in order to have approximately the same definition of atopic sensitization in the combined group. We also adjusted for group sample in this model, to investigate if whether this variable was a significant predictor of GI complaints.

GI complaints were found to be significantly associated with total IgE (b = .037, p = .001), and inversely significantly associated with atopic sensitization (b = -33.855, p < .001) when adjusting for group sample status, in addition to sex and age (table 5). The estimate of the association

between GI complaints and total IgE was similar to the estimates previously found in the patient group and general population when analyzed separately.

According to the multiple regression analysis (table 5), the group sample variable was significantly associated with GI complaints, whereas patients on average reported more GI complaints than the general population (b = 115.888, p < .001). We therefore performed a regression analysis in order to test if there was a significant interaction effect of IgE and group sample on GI complaints. No significant interaction was found (p = .395), implying that the association between total IgE and GI complaints was not significantly different in the two samples (patient group and general population).

4.5 Stratified sampling and analysis of interaction by gender and atopic status

Stratified sampling according to gender was performed in order to investigate whether the associations of GI complaints with total IgE levels differed between men and women.

Table 6: The association between GI complaints (IBS-SSS) and total IgE in men (n = 296) and women (n = 304), analyzed with multiple regression analysis and adjusted for *atopic sensitization, age and sample.

Subgroup	Direct effect of total IgE on IBS-SSS b (95% CI)	p-value
Men	.026 (-.003, .056)	.079
Women	.045 (.013, .078)	.006

The following symbol represent: b = unstandardized beta coefficient.
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) among patients and as having elevated specific IgE (> 0.35kU/L) to grass, cat or *Dermatophagoides pteronyssinus* in the general population.

Similarly, stratified sampling were computed according to atopic status among the included participants, with the intention to investigate if the association between total IgE and GI complaints differed between atopic and non-atopic individuals.

Table 7: The association between GI complaints (IBS-SSS) and total IgE in atopic individuals (n = 202) and non-atopic individuals (n = 398), analyzed with multiple regression and adjusted for sex, age and sample.

Subgroup	Direct effect of total IgE level on IBS-SSS b (95% CI)	p-value
Atopic	.040 (.014, .065)	.003
Non-atopic	.044 (-.029, .118)	.236

The following symbol represent: b = unstandardized beta coefficient

According to table 6 and 7, we see approximately the same consistent direct effect of total IgE on GI complaints in all stratified samplings. We performed a regression analysis to test if there was a significant interaction effect of IgE and gender on GI complaints in addition to the direct effect of IgE controlled for the other explanatory variables used previously. Women had more GI complaints than men, but the interaction effect was not significant ($p = .721$), indicating that the associations between total IgE and GI complaints (IBS-SSS) were not different in men and women. Correspondingly, a regression analysis was performed in order to examine if there was a significant interaction effect of IgE and atopic sensitization on GI complaints. No significant interaction effect was found ($p = .556$), suggesting that the effect of IgE on GI complaints was evenly distributed between atopic and non-atopic individuals.

Furthermore, we performed stratified sampling according to age. We divided the total study population into two age subgroups, i.e. participants aged under 50 (range: 15 - 49) and participants aged over 50 (range: 50 - 75). Multiple regression analyzes performed in these subgroups are presented in the following table (table 8).

Table 8: The association between GI complaints (IBS-SSS) and total IgE in participants aged under 50 (n = 286) and over 50 (n = 314), analyzed with multiple regression and adjusted for *atopic sensitization, sex and sample.

Subgroup	Direct effect of total IgE level on IBS-SSS b (95% CI)	p-value
Individuals aged under 50	.050 (.018, .082)	.002
Individuals aged over 50	.020 (-.010, .049)	.191

The following symbol represent: b = unstandardized beta coefficient
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) in patients and as having elevated specific IgE (> 0.35kU/L) to grass, cat or *Dermatophagoides pteronyssinus* among the general population.

We performed a regression analysis to test whether there was a significant interaction effect of IgE and age on GI complaints. We observed that the younger participants had more GI complaints than the elder, however the difference was not significant (p = .241), indicating that the effect of total IgE on GI complaints was evenly distributed between respondents with different age.

Thus, the association between total IgE and GI complaints appeared to be consistent in all subgroups, with no significant differences according to gender, atopic status, or age.

In addition, we performed analogous regression analyzes to test if there was a significant interaction effect of atopic sensitization and gender, or atopic sensitization and age, on GI complaints. The interaction effect of atopic sensitization and gender was not significant (p = .526). Neither did we find any significant interaction effect of atopic sensitization and age on GI complaints (p = .162). Hence, we verified that the negative association between atopic sensitization and GI complaints was not significantly influenced by gender or age.

DISCUSSION

5.1 Summary

To our knowledge, this is the first study where the association between total IgE levels, atopic sensitization and food-related GI complaints (symptoms of IBS) has been investigated. Our main aim was to investigate the relationship between total IgE, atopic sensitization and GI complaints. IBS-SSS and IBS-SQ were thus used as diagnostic tools to address the severity of GI complaints in the current study. We hypothesized that total IgE and atopic sensitization would be positively associated with GI complaints, in accordance with previous studies revealing increased number of "IgE-armed" mast cells in duodenal mucosa of patients with food hypersensitivity (3). Our results indicated that both total IgE levels and atopic sensitization were higher in patients and there was a positive, but non- significant, association between GI symptoms and total IgE in patients, whereas this association was significant in the general population. Also, we found that there was a negative relationship between GI symptoms and atopic sensitization, which was significant in the patient group, indicating no vital role of allergic sensitization in the actual development of unexplained SFH. When analyzing men and women separately, we found similar consistent associations between total IgE and GI complaints. This was also the same when we analyzed the participants according age, whereas we separated the participants in two age groups. We detected the same tendencies in the patient group and in the general population, and also among atopic and non-atopic, thus the association of GI complaints with higher IgE levels was a consistent finding. However, total IgE and atopic sensitization could together explain a relatively small proportion of the total variance in GI complaints in both study populations (6.2 % and 1.9 %, respectively).

5.2 Results from study

In this study we found that abdominal pain and discomfort were the most prominent GI complaints among patients (76.4 %) followed by bloating (61.5 %) and change in frequency of stool (59.0 %), whereas bloating was most common in the general population, affecting 41.3 %. These observations are consistent with previous findings in patients with SFH, whereas abdominal pain and discomfort are the predominant GI symptoms (1, 18, 33). Interestingly, we

also observed a high prevalence of GI complaints in our patient subgroup referred to allergological examination with other allergic symptoms as primary cause of reference. Both patient subgroups had higher prevalence of atopic sensitization compared to the general population. However, total IgE levels and prevelance of atopic sensitization were higher in the patient subgroup with other complaints as primary cause of reference, than in the patient subgroup with GI complaints. This also suggests that even though these two patient subgroups have different primary causes for referring to Section of Clinical Allergology, patients with other allergic symptoms as predominant also have symptoms of IBS in addition to higher levels of total IgE and atopic sensitization.

Timothy, birch and dog were the most common inhalant allergens in patient group, whereas hazelnut, wheat and peanut were the most common food allergens. This corresponds with previous findings in patients reporting food hypersensitivity (3, 18). Although we demonstrated that atopic sensitization was negatively associated with GI complaints, the association between levels of specific IgE to the selected food allergens and GI complaints are interesting topics for further research.

The various GI complaints reported among the included participants in this study were compatible with IBS symptoms, and we found that 71.4 % of the patients had IBS, whereas 20.5 % had symptoms of severe IBS. In the selected patient subgroups, 91.4 % had IBS in the group comprising patients with GI complaints as primary cause of reference. Surprisingly, over half of the patients comprising the second patient subgroup also had symptoms of IBS in addition to other allergic symptoms. It is also interesting that this group consisted of patients with the highest levels of total IgE and the highest prevalence of atopic individuals, indicating a potential link between these variables and GI symptoms. The two patient subgroups were initially categorized based on referral reason and to demographically describe the different patients, but considering the analyzes of relationship between total IgE or atopic sensitization and GI complaints, this division of patients was not of interest, and we therefore merged the two subgroups in one patient group. In the general population, one third had IBS, however most of these individuals had a mild form of IBS, whereas only 1.88 % suffered from severe IBS, indicating that GI complaints did not have any major impact in these participants daily life. In the patient group 22.98% had no symptoms of IBS, while 62.34 % had no symptoms of IBS in the general population.

The patient group was considered as an atopic group with a high prevalence of atopic sensitization, and levels of total IgE were significantly higher in patients compared to the general population group. There was no significant correlation between total IgE and GI complaints specified as IBS-SSS and IBS-SQ in the patient group. However, in the general population group there was a significant correlation between total IgE and IBS-SSS, but not between total IgE and IBS-SQ. This difference observed in significant values was most likely due to the different group sizes, where the general population group is a much larger sample.

A significant difference was observed between atopic and non-atopic patients according to IBS-SSS, where non-atopic on average reported more GI complaints than atopic in patient group. The same tendency was seen in general population, but the means were not significantly different between atopic and-non atopic individuals. The different definitions of atopic sensitization in the two groups were likely to be the cause of difference in significant values. In patient group, the only variable accounting for significant effect in multiple regression analysis was atopic sensitization, defined as elevated levels of specific IgE to at least one allergen. Total IgE was not significantly associated with GI complaints in this group. Same indications were observed in general population, where total IgE was significantly associated with GI complaints. The effect of atopic sensitization was not significant in this group, however this might be because atopic sensitization was defined different in this group. In the current study, total IgE and atopic sensitization could together explain 6.2 % and 1.9% of total variance in GI complaints in the patient group and general population respectively.

We found the same tendencies in both the patient group and the general population, where total IgE significantly correlated with GI complaints in the general population sample. Also, similar results were observed according to the association between GI complaints and atopic sensitization, in which atopy appeared to have an inverse effect on GI symptoms in both groups as non-atopic persons have more GI complaints. We therefore combined the patient group and the general population in one merged group, in order to observe the variable's effects in a larger sample. Every explanatory variable, with the exception of sex, was significantly associated with GI complaints in the combined group comprising all participants, whereas atopic sensitization had the greatest effect. This observation in a total study population supported our previous findings.

According to our stratified and interaction analyzes, there were not observed any significant interaction effects of gender or age when it came to the association between total IgE or atopic sensitization and GI complaints respectively.

GI disorders are very common in the western civilization, and patients reporting GI complaints self-attributed to food items comprise a selected group. The GI symptoms reported by these patients after consumption of food are often compatible with IBS, and according to the Rome criteria many of these patients are diagnosed IBS (1, 18). The pathophysiology of IBS is yet not well understood, however several mechanisms are suggested. It is observed that consumption of low digestible carbohydrates, such as FODMAPs, triggers GI complaints and may worsen the situation. Subsequent bacterial fermentation in the colon could cause excess amounts of intestinal gas and distention, in which is a major contributor of abdominal pain and discomfort (15, 37, 38, 63). Also, the role of the gut microbiota is recognized as vital, whereas bacterial dysbiosis or changes in the intestinal micro flora is known to cause GI complaints (21, 47, 64). Often, patients reporting severe GI illnesses are recognized as psychosomatic, and therefore many are referred to a psychologist in attempt to offer these patients treatment. However, a study from MAI team demonstrated that psychological factors were not major predictors of GI symptoms in patients reporting food hypersensitivity (29).

5.3 Limitation of study and methodological issues

5.3.1 Participants and design of study

The two groups included in this study were somewhat different, whereas the general population was a much larger sample. The effect of this was two-sided, whereas the large group sample of the general population contributed to strengthen our results, however it also made it somewhat difficult to compare the two groups in an overall perspective. Regarding the general population sample, it is important to have in mind that the participants in the general population were not defined as healthy controls, but as representatives of general population. The different age ranges were also set to be different among the two groups, whereas the general population consisted of elder people than the patient group. Because of missing data of specific IgE to food allergens and certain inhalant allergens in the general population, the definition of atopic sensitization was to some extent different in the two groups.

5.3.2 Use of IBS-SSS and IBS-SQ in a general population

The IBS-SSS and IBS-SQ questionnaires are developed for use in patient populations with GI complaints. In a general population, subjects with no such complaints often did not answer the questions. Missing information was thus re-coded as "no". The misclassification introduced by this is likely to have attenuated associations.

5.3.3 Food allergens and GI complaints

In the current study, we did not investigate the association between the severity of GI complaints and positive specific IgE levels to specific food allergens, such as cow`s milk, milk protein, gluten and wheat in the selected groups. This should be followed up in additional studies on the pathophysiology of food hypersensitivity and IBS.

5.3.4 Data collection

Due to the large timeframe, comprising over 2 years, of this study, there have been several different allergologic physicians responsible for the data collection in the patient group. This may contribute to random errors on the collected patient material, especially when it comes to the primary cause of reference in the two patient subgroups.

5.4 Reflections on findings

The prevalence of atopic diseases among patients with GI disorders, including IBS, is highly recognized (3, 7, 14, 65, 66), and *vice versa,* GI symptoms are frequently reported in allergic individuals, thus potential links between atopic disorders and GI diseases are proposed (67). Mast cells have also been suggested to play a key role in the development of GI disorders, including inflammatory bowel disease and IBS (53, 68), and O'Sullivan et al. found in a study from 2000 a significantly increased number of colonic mast cells in IBS patients, compared to controls (69). Interestingly, they found in a study from MAI team that the number of duodenal IgE-positive cells were significantly higher in atopic patients than in non-atopic, in which

appeared to be "IgE-armed" mast cells (3). The atopic patients also had increased intestinal permeability when compared with non-atopic patients. These observations of histological changes in the GI region of patients with allergic diseases are consistent with some previous investigations (4-6, 70). Thus, according to various studies, "atopic IBS" was recently proposed as a new subgroup of IBS, with a distinct role of activated mast cells (3, 7), and identifying atopy in patients with IBS symptoms was suggested as an important link in elucidating the pathophysiology of IBS. The following study demonstrated that levels of total IgE were significantly associated with GI complaints in a general population, suggesting a pathological link between food-related IBS-symptoms and increased levels of total IgE. Atopic sensitization appeared to have no vital influence on GI symptoms in both group samples, in contrast to previous studies linking atopic diseases and IBS. In fact, our results indicated a significant negative association between atopic sensitization and GI complaints among patients, contrary to our initiated hypothesis. Together, total IgE and atopic sensitization could explain only a small proportion of GI complaints, i.e. 6.2 % and 1.9 % in patient group and general population, respectively. These observations support that specific IgE-mediated processes appear to have little impact on IBS-like complaints, and that atopic sensitization and/or allergy play a small role in the actual development of food-related GI complaints. Although patients with IBS previously have been shown to have an increased number of mast cells located in the gut, it is not anticipated that classical IgE-mediated sensitization is the cause of GI symptoms (53, 69, 71). Mast cells encompass membrane IgE receptors, capable of attaching circulating IgE antibodies, and in accordance to the documentation of a significant correlation between IgE-armed mast cells and serum total IgE by Lillestøl et al., it is conceivable that the increased number of mucosal armed mast cells induce intestinal hypersensitive to a variety of mechanical stimuli, including bloating, distension and water retention (3). Visceral hypersensitivity is commonly found in patients with IBS, and several studies indicate abdominal symptom relief after mast cell stabilizer administration (72). Whether the cause of the increased number of IgE-cased mast cells in intestinal mucosa is in concordance with increased levels of total IgE in serum is yet uncertain, and we do not know if this discovery revealing total IgE as a significant predictor of GI complaints in a general population is yet of clinical significance. However we do believe that the term "atopic bowel" may be of particularly interest in patients with high total IgE in serum.

Conversely, the actual role of total IgE levels in serum in the development of food-related GI complaints and IBS must be investigated further by mechanistic and epidemiological studies in order to clarify whether high total IgE a primary or secondary cause of IBS. Also, conditions

which contributes to elevated levels of total IgE are interesting topics for further research. Parasitic infections in human are persuasive stimulus for IgE production, and helminth parasites are considered as one of the most potent invasive infections leading to synthesis of IgE antibodies and elevated levels of serum total IgE (73). Helminths represent one of the most prevalent form if parasitic infections in human, often resident in the GI tract, whereas food items and poorly washed vegetables are one of the major sources (74). Levels of serum total IgE have also been associated with asthma and reduced pulmonary function. Haselkorn et al. demonstrated in a study from 2010 a significant association between high levels of serum total IgE and reduced lung capacity, indicating a link between asthma severity and elevated serum total IgE (57). Also, in a more recently study from 2013, Arroyave et. al reported that increased serum specific IgE levels to particular indoor environmental allergens was strongly correlated with increased severity of asthma (75).

Evidence from the current study support that levels of total IgE and atopic sensitization could together explain a relatively small proportion of the total variance in GI complaints, whereas approximately 94% of the total variance in symptom severity remains unexplained. This also supports that other mechanisms are involved in pathophysiology and symptom generation of IBS. Therefore, in future other causal factors, such as intestinal bacteria flora and fermentation issues, should be of interest when investigating the underlying contributory mechanisms of IBS. Also, the inversely association between atopic sensitization and GI complaints show that food-related symptoms of IBS are not mediated by specific IgE-mediated processes. Nevertheless, even though levels of total IgE and atopy probably play little role, the importance of other immunological factors such as toll-like receptors and cytokines, and its relation with gut microbiota should be further researched.

6. CONCLUSION

The overall findings from our results are as follows:

1. Total IgE and atopic sensitization were significantly more common in patients referred for GI complaints than in a general population.

2. Levels of total IgE was a significant predictor of GI complaints.

3. Atopic sensitization was inversely related to GI complaints.

4. Together, total IgE and atopic sensitization could explain a relatively small proportion of the total variance in GI complaints in both patient group and the general population.

5. There were no significant interaction effects by gender, age, sample or atopic sensitization in the association between total IgE and GI complaints. This association appeared to be consistent in all these subgroups.

The findings indicating that total IgE is a consistent predictor of GI complaints are very interesting. Although the effect of total IgE appeared to be small, the association is considered highly relevant and supports a role for total IgE-related immunology in the pathophysiology of food related symptoms of IBS. Whether elevated levels of total IgE is related to duodenal "IgE-armed" mast cells remains uncertain, though it is a hypothetical possibility and should be further investigated. In addition, the results regarding atopic sensitization and GI complaints presented in this study indicate that GI symptoms self-attributed to food are not mediated by specific IgE-mediated processes. Consequently, biological mechanisms constituting increased levels of total IgE (with the exception of specific IgE) are very interesting topics for further research on the pathophysiology of food-related GI complaints.

REFERENCES

1. 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. Dig Dis Sci. 2004;49(4):680-7. Epub 2004/06/10.

2. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol. 2007;120(3):638-46. Epub 2007/07/14.

3. Lillestol K, Helgeland L, Arslan Lied G, Florvaag E, Valeur J, Lind R, et al. Indications of 'atopic bowel' in patients with self-reported food hypersensitivity. Aliment Pharmacol Ther. 2010;31(10):1112-22. Epub 2010/02/19.

4. Kalimo K, Lammintausta K, Klemi P, Leino R, Panula P, Kalimo H. Mast cells and IgE in intestinal mucosa in adult atopic dermatitis patients. Br J Dermatol. 1988;119(5):579-85. Epub 1988/11/01.

5. Magnusson J, Lin XP, Dahlman-Hoglund A, Hanson LL, Telemo E, Magnusson O, et al. Seasonal intestinal inflammation in patients with birch pollen allergy. J Allergy Clin Immunol. 2003;112(1):45-50. Epub 2003/07/09.

6. Pires GV, Souza HS, Elia CC, Zaltman C, Carvalho AT, Tortori CJ, et al. Small bowel of patients with asthma and allergic rhinitis: absence of inflammation despite the presence of major cellular components of allergic inflammation. Allergy Asthma Proc. 2004;25(4):253-9. Epub 2004/10/30.

7. Tobin MC, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. Ann Allergy Asthma Immunol. 2008;100(1):49-53. Epub 2008/02/08.

8. O'Leary PF, Shanahan F. Food allergies. Curr Gastroenterol Rep. 2002;4(5):373-82. Epub 2002/09/14.

9. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-6. Epub 2004/05/08.

10. Bogen B, Munthe LA. Immunologi. 2. utg. ed. Oslo: Universitetsforl.; 2007. 334 s. p.

11. Lind R, Kahrs G. Matoverfølsomhet hos voksne med mage- og tarmplager. Utposten. 2007;5:41-7.

12. Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. Gastroenterology. 1992;103(3):1075-95. Epub 1992/09/01.

13. Begin P, Nadeau KC. Diagnosis of food allergy. Pediatr Ann. 2013;42(6):102-9. Epub 2013/05/31.

14. Zar S, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. Aliment Pharmacol Ther. 2001;15(4):439-49. Epub 2001/04/04.

15. Lied GA, Lillestol K, Lind R, Valeur J, Morken MH, Vaali K, et al. Perceived food hypersensitivity: a review of 10 years of interdisciplinary research at a reference center. Scand J Gastroenterol. 2011;46(10):1169-78. Epub 2011/06/18.

16. Sampson HA, Anderson JA. Summary and recommendations: Classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. J Pediatr Gastroenterol Nutr. 2000;30 Suppl:S87-94. Epub 2000/01/14.

17. Lind R, Kahrs G. Matoverfølsomhet hos voksne med mage- og tarmplager. Utposten. 2007;5:41-5.

18. Arslan G, Kahrs GE, Lind R, Froyland L, Florvaag E, Berstad A. Patients with subjective food hypersensitivity: the value of analyzing intestinal permeability and inflammation markers in gut lavage fluid. Digestion. 2004;70(1):26-35. Epub 2004/08/07.

19. Hillilä M. Irritable bowel syndrome in the general population: epidemiology, comorbidity, and societal costs Helsinki, Finland: Helsinki University Central Hospital; 2010.

20. Moriarty KJ, Vandvik PO, Landsforeningen mot fordøyelsessykdommer. Forstå irritabel tarm. Oslo: Exlibris; 2007. 144 s. p.

21. Collins SM, Denou E, Verdu EF, Bercik P. The putative role of the intestinal microbiota in the irritable bowel syndrome. Dig Liver Dis. 2009;41(12):850-3. Epub 2009/09/11.

22. Abraczinskas D, Goldfinger SE. Intestinal gas and bloating. UpToDate. 2007.

23. Murray CD, Flynn J, Ratcliffe L, Jacyna MR, Kamm MA, Emmanuel AV. Effect of acute physical and psychological stress on gut autonomic innervation in irritable bowel syndrome. Gastroenterology. 2004;127(6):1695-703. Epub 2004/12/04.

24. Lind R, Arslan G, Eriksen HR, Kahrs G, Haug TT, Florvaag E, et al. Subjective health complaints and modern health worries in patients with subjective food hypersensitivity. Dig Dis Sci. 2005;50(7):1245-51. Epub 2005/07/29.

25. Arebi N, Gurmany S, Bullas D, Hobson A, Stagg A, Kamm M. Review article: the psychoneuroimmunology of irritable bowel syndrome--an exploration of interactions between psychological, neurological and immunological observations. Aliment Pharmacol Ther. 2008;28(7):830-40. Epub 2008/07/19.

26. Jarrett M, Visser R, Heitkemper M. Diet triggers symptoms in women with irritable bowel syndrome. The patient's perspective. Gastroenterol Nurs. 2001;24(5):246-52. Epub 2002/02/19.

27. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? Lancet. 2002;360(9332):555-64. Epub 2002/09/21.

28. Lillestol K, Berstad A, Lind R, Florvaag E, Arslan Lied G, Tangen T. Anxiety and depression in patients with self-reported food hypersensitivity. Gen Hosp Psychiatry. 2010;32(1):42-8. Epub 2010/02/02.

29. Lind R, Lied GA, Lillestol K, Valeur J, Berstad A. Do psychological factors predict symptom severity in patients with subjective food hypersensitivity? Scand J Gastroenterol. 2010;45(7-8):835-43. Epub 2010/05/04.

30. Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quartero AO. Psychological treatments for the management of irritable bowel syndrome. Cochrane Database Syst Rev. 2009(1):CD006442. Epub 2009/01/23.

31. Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2005(2):CD003460. Epub 2005/04/23.

32. Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. Scand J Psychol. 2002;43(2):113-21. Epub 2002/05/15.

33. Lied GA, Vogelsang P, Berstad A, Appel S. Dendritic cell populations in patients with self-reported food hypersensitivity. Int J Gen Med. 2011;4:389-96. Epub 2011/06/01.

34. Lied GA, Lillestol K, Valeur J, Berstad A. Intestinal B cell-activating factor: an indicator of non-IgE-mediated hypersensitivity reactions to food? Aliment Pharmacol Ther. 2010;32(1):66-73. Epub 2010/04/01.

35. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. J Gastroenterol Hepatol. 2010;25(2):252-8. Epub 2010/02/09.

36. Heizer WD, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. J Am Diet Assoc. 2009;109(7):1204-14. Epub 2009/06/30.

37. Valeur J, Morken MH, Norin E, Midtvedt T, Berstad A. Carbohydrate intolerance in patients with self-reported food hypersensitivity: comparison of lactulose and glucose. Scand J Gastroenterol. 2009;44(12):1416-23. Epub 2009/11/04.

38. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. J Am Diet Assoc. 2006;106(10):1631-9. Epub 2006/09/27.

39. Gregersen K, Lind RA, Valeur J, Bjorkkjaer T, Berstad A, Lied GA. Duodenal administered seal oil for patients with subjective food hypersensitivity: an explorative open pilot study. Int J Gen Med. 2010;3:383-92. Epub 2010/12/31.

40. Treem WR, Ahsan N, Kastoff G, Hyams JS. Fecal short-chain fatty acids in patients with diarrhea-predominant irritable bowel syndrome: in vitro studies of carbohydrate fermentation. J Pediatr Gastroenterol Nutr. 1996;23(3):280-6. Epub 1996/10/01.

41. Hanevik K, Dizdar V, Langeland N, Hausken T. Development of functional gastrointestinal disorders after Giardia lamblia infection. BMC Gastroenterol. 2009;9:27. Epub 2009/04/23.

42. Gregersen K, Froyland L, Berstad A, Araujo P. Direct determination of serotonin in gut lavage fluid by liquid chromatographic ion trap tandem mass spectrometry. Talanta. 2008;75(2):466-72. Epub 2008/03/29.

43. Garvin B, Wiley JW. The role of serotonin in irritable bowel syndrome: implications for management. Curr Gastroenterol Rep. 2008;10(4):363-8. Epub 2008/07/17.

44. Gregersen K, Valeur J, Lillestol K, Froyland L, Araujo P, Lied GA, et al. Subjective food hypersensitivity: assessment of enterochromaffin cell markers in blood and gut lavage fluid. Int J Gen Med. 2011;4:555-60. Epub 2011/09/03.

45. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000;95(12):3503-6. Epub 2001/01/11.

46. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. J Clin Gastroenterol. 2010;44(10):672-5. Epub 2010/09/15.

47. Quigley EM. Do Patients with Functional Gastrointestinal Disorders have an Altered Gut Flora? Therap Adv Gastroenterol. 2009;2(4):23-30. Epub 2009/07/01.

48. Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, et al. Effect of multi-species probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol. 2013. Epub 2013/07/09.

49. Borody TJ, Warren EF, Leis SM, Surace R, Ashman O, Siarakas S. Bacteriotherapy using fecal flora: toying with human motions. J Clin Gastroenterol. 2004;38(6):475-83. Epub 2004/06/29.

50. Drossman DA. The functional gastrointestinal disorders and the Rome II process. Gut. 1999;45 Suppl 2:II1-5. Epub 1999/08/24.

51. Pimentel M, Talley NJ, Quigley EM, Hani A, Sharara A, Mahachai V. Report from the multinational irritable bowel syndrome initiative 2012. Gastroenterology. 2013;144(7):e1-5. Epub 2013/05/07.

52. Arslan G, Odegaard S, Elsayed S, Florvaag E, Berstad A. Food allergy and intolerance: response to intestinal provocation monitored by endosonography. Eur J Ultrasound. 2002;15(1-2):29-36. Epub 2002/06/05.

53. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004;126(3):693-702. Epub 2004/02/28.

54. Carroll WD, Lenney W, Child F, Strange RC, Jones PW, Whyte MK, et al. Asthma severity and atopy: how clear is the relationship? Arch Dis Child. 2006;91(5):405-9. Epub 2006/01/31.

55. Peat JK, Toelle BG, Dermand J, van den Berg R, Britton WJ, Woolcock AJ. Serum IgE levels, atopy, and asthma in young adults: results from a longitudinal cohort study. Allergy. 1996;51(11):804-10. Epub 1996/11/01.

56. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med. 1991;325(15):1067-71. Epub 1991/10/10.

57. Haselkorn T, Szefler SJ, Simons FE, Zeiger RS, Mink DR, Chipps BE, et al. Allergy, total serum immunoglobulin E, and airflow in children and adolescents in TENOR. Pediatr Allergy Immunol. 2010;21(8):1157-65. Epub 2010/05/07.

58. Park MI. Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review. Neurogastroenterol Motil. 2006;18:595-607.

59. Bartra J, Sastre J, del Cuvillo A, Montoro J, Jauregui I, Davila I, et al. From pollinosis to digestive allergy. J Investig Allergol Clin Immunol. 2009;19 Suppl 1:3-10. Epub 2009/05/30.

60. Matsui EC, Sampson HA, Bahnson HT, Gruchalla RS, Pongracic JA, Teach SJ, et al. Allergen-specific IgE as a biomarker of exposure plus sensitization in inner-city adolescents with asthma. Allergy. 2010;65(11):1414-22. Epub 2010/06/22.

61. Kane SV, Sandborn WJ, Rufo PA, Zholudev A, Boone J, Lyerly D, et al. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. Am J Gastroenterol. 2003;98(6):1309-14. Epub 2003/06/24.

62. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997;11(2):395-402. Epub 1997/04/01.

63. Haderstorfer B, Psycholgin D, Whitehead WE, Schuster MM. Intestinal gas production from bacterial fermentation of undigested carbohydrate in irritable bowel syndrome. Am J Gastroenterol. 1989;84(4):375-8. Epub 1989/04/01.

64. Cremon C, Carini G, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G. Intestinal dysbiosis in irritable bowel syndrome: etiological factor or epiphenomenon? Expert Rev Mol Diagn. 2010;10(4):389-93. Epub 2010/05/15.

65. Stefanini GF, Saggioro A, Alvisi V, Angelini G, Capurso L, di Lorenzo G, et al. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. Scand J Gastroenterol. 1995;30(6):535-41. Epub 1995/06/01.

66. Stefanini GF, Prati E, Albini MC, Piccinini G, Capelli S, Castelli E, et al. Oral disodium cromoglycate treatment on irritable bowel syndrome: an open study on 101 subjects with diarrheic type. Am J Gastroenterol. 1992;87(1):55-7. Epub 1992/01/01.

67. Powell N, Huntley B, Beech T, Knight W, Knight H, Corrigan CJ. Increased prevalence of gastrointestinal symptoms in patients with allergic disease. Postgrad Med J. 2007;83(977):182-6. Epub 2007/03/09.

68. Gui XY. Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome. J Gastroenterol Hepatol. 1998;13(10):980-9. Epub 1998/12/03.

69. O'Sullivan M, Clayton N, Breslin NP, Harman I, Bountra C, McLaren A, et al. Increased mast cells in the irritable bowel syndrome. Neurogastroenterol Motil. 2000;12(5):449-57. Epub 2000/09/30.

70. Dunlop SP, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. Am J Gastroenterol. 2006;101(6):1288-94. Epub 2006/06/15.

71. Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, et al. The immune system in irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17(4):349-59. Epub 2011/12/08.

72. Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Gut. 2010;59(9):1213-21. Epub 2010/07/24.

73. Jarrett E, Bazin H. Elevation of total serum IgE in rats following helminth parasite infection. Nature. 1974;251(5476):613-4. Epub 1974/10/18.

74. Watkins WE, Pollitt E. "Stupidity or worms": do intestinal worms impair mental performance? Psychol Bull. 1997;121(2):171-91. Epub 1997/03/01.

75. Arroyave WD, Rabito FA, Carlson JC. The Relationship Between a Specific IgE Level and Asthma Outcomes: Results from the 2005-2006 National Health and Nutrition Examination Survey. J Allergy Clin Immunol Pract. 2013;1(5):501-8. Epub 2014/02/26.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:		Vår dato:	Vår referanse:
REK vest	Anne Berit Kolmannskog	55978496		28.06.2011	2011/1118/REK vest
				Deres dato:	**Deres referanse:**
				10.05.2011	

Vår referanse må oppgis ved alle henvendelser

Gülen Arslan Lied
gulen.arslan@med.uib.no
Haukeland Universitetssykehus

2011/1118 Har serum total IgE nivå noen virkning på gastrointestinale plager hos pasienter med selvrapportert matoverfølsomhet?

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk i møtet 09.06.2011.

Prosjektomtale (revidert av REK):
REK Vest anser Helse Bergen HF som forskningsansvarlig for prosjektet. Formålet med denne studien er å se om det finnes en sammenhengen mellom atopisk sykdom, som pollenallergi, og mage-tarmproblemer blant pasienter med matoverfølsomhet. Indikasjon på atopisk sykdom er påvist blant mange med
mage-tarmproblematikk. Det er derfor av interesse å se om atopi inkludert atopisk tarm og pollensesongen har noen innvirkning på mage-tarmplager hos disse pasientene. Pasienter som er henvist til Seksjon for Spesialallergologi, Yrkesmedisinsk avdeling, Haukeland universitetssykehus med mistanke om allergisk sykdom med og uten mage-tarm plager vil bli forespurt om å delta. Demografiske data, alder, kjønn og etnisk rase samt informasjoner om atopi, allergiske sykdommer og mage-tarm plager vil bli registrert. Det vil bli tatt blodprøve og utføres hudprikkstest. Forskningsdata fra kontrollgruppen vil hentes fra en tidligere godkjent studie, ECRHS III 2010/759

Forskningsetisk vurdering
Komiteen anser prosjektet som uproblematisk og har ingen større innvendinger til forelagt protokoll.

Kontrollgruppen
En ønsker å innhente data og biologisk materiale fra en kontrollgruppe som rekrutteres gjennom en annen tidigere godkjent studie (2010/759). Komiteen har ingen innvendinger til dette og legger til grunn at prosjektene har sammenfallende problemstillinger som ikke utløser krav til nytt samtykke fra kontrollgruppen (jf helseforskningsloven § 15).

Etnisistet
Spørsmål om etnisitet er å anse som sensitiv informasjon.
Komiteen legger til grunn at en i dette prosjektet har faglige og vitenskaplige grunner for å be om at pasientene oppgir sin etnisitet/rase.

Forskningsbiobank
Komiteen legger til grunn at det skal samles biologisk materialet og at det er behov for en

forskningsbiobank tilknyttet studien. Dersom det biologiske materialet ikke skal lagres etter at analysene er gjennomført er det ikke behov for biobank. Komiteen ber om at det opplyses om behovet for biobank gjennom en endringsmelding slik at den opprettede biobanken kan avvikles dersom det ikke er behov for den.

Informasjonsskrivet
Informasjonsskrivet må språkvaskes og forenkles slik at språket tilgjengliggjør innholdet i forespørselen. Fremmedord og fagterminologi må forenkles.
Inklusjon avhenger av hvor mange som svarer ja til å delta og følgende setning i informasjonsskrivet må modereres. "I løpet av ett års tid skal alle pasienter som er henvist til Seksjon for Spesialallergologi, Yrkesmedisin, HUS på grunn av mistanke om allergisk sykdom med og uten mage-tarm plager bli inkludert i studie."

Datasikkerhet
REK Vest ber om at lagrede forskningsdata og materiale følger Helse Bergen HF sin internrutiner, og forutsetter at deres forskningsserver benyttes.
Prosjektslutt er satt til 31.08.2012. Personidentifiserbare forskningsdata skal anonymiseres eller slettes straks det ikke lenger er behov for dem og senest 5 år etter prosjektslutt.

Vedtak
1. *Prosjektet godkjennes på betingelse av at ovennevnte vilkår tas til følge.*
2. *Forskningsbiobanken "Serum total IgE nivå og gastrointestinale plager" godkjennes på betingelse av at ovennevnte vilkår tas til følge. Godkjenningen gjelder inntil 5 år etter prosjektets avslutning.*

Prosjektet skal sende sluttmelding til REK vest på fastsatt skjema senest 28.02.2013.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no.
Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Jon Lekven (sign.)
komiteleder

Anne Berit Kolmannskog
sekretariatsleder

Kopi til: postmottak@helse-bergen.no

Saksbehandlingen følger forvaltningsloven. Komiteenes vedtak etter forskningsetikklovens § 4 kan påklages (jfr. forvaltningsloven § 28) til Den nasjonale forskningsetiske komité for medisin og helsefag. Klagen skal sendes REK Vest (jfr. forvaltningsloven § 32). Klagefristen er tre uker fra den dagen du mottar dette brevet (jfr. forvaltningsloven § 29).

De regionale komiteene for medisinsk og helsefaglig forskningsetikk foretar sin forskningsetiske vurdering med hjemmel i helseforskningsloven § 10, jfr. forskningsetikkloven § 4. REK Vest forutsetter at dette vedtaket blir forelagt den forskningsansvarlige til orientering. Se helseforskningsloven § 6, jfr. § 4 bokstav e.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no. Vennligst oppgi vårt referansenummer i korrespondansen

Forespørsel om deltakelse i forskningsprosjektet

Har serum total IgE nivå noen virkning på gastrointestinale plager hos pasienter med selvrapportert matoverfølsomhet?

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å se om det er noen sammenheng mellom serum total IgE nivå og mage-tarm plager hos pasienter med selvrapportert matoverfølsomhet. Mage-tarm plager er vanlig og ofte selv attributt til matoverfølsomhet hos generell befolkningen. Selv om opp til 35% av befolkningen rapporterer om unormale reaksjoner på en eller flere typer matvarer, så er det bare 1-3 prosent av de voksne som får diagnostisert "ekte" matallergi.

Selv om pasientene sjelden hadde tegn til klassisk IgE-mediert matallergi, fant vi i tidligere studier interessante sammenhenger knyttet til nivået av total IgE i serum. Dette var ofte høyt hos pasientene og pasienter med høyt total IgE hadde også ofte høyt antall mastceller med adherent IgE i biopsier fra tynntarmslimhinnen. Der var således en høygradig signifikant korrelasjon mellom serum total IgE og antall "armerte" mastceller. Over 60% av pasientene hadde indikasjon på atopisk sykdom (forhøyet total IgE, funn av spesifikk IgE i serum og/eller positiv prikktest, atopisk sykehistorie som allergisk rhinitt, eksem, eller astma). Atopisk pasienter hadde også økt intestinal permeabilitet og høy antall av IgE positive celler i tynntarmslimhinnen enn ikke-atopiske pasienter. Derfor er det interessant å se om atopi inkludert atopisk tarm og pollensesongen har noen virkning på mage-tarm plager hos disse pasienter.

Hovedhensikten med denne studien er å undersøke om det er noen sammenheng mellom serum total IgE nivå inkludert serum spesifikk-IgE og hudprikktest og gastrointestinale plager, og å se dens relasjon til pollensesongen for å identifisere atopiens rolle ved utvikling av mat-relaterte magetarm-plager.

Hva innebærer studien?

I løpet av ett års tid skal alle pasienter som er henvist til Seksjon for Spesialallergologi, Yrkesmedisin, HUS på grunn av mistanke om allergisk sykdom med og uten mage-tarm plager bli inkludert i studie. I tillegg skal en kontrollgruppe fra den generelle befolkningen bli inkludert. De demografiske dataene alder, kjønn og etisk rase fra alle pasienter og kontrollgruppe skal registreres i en database, og de vil delta i "allergologiske screening" inkludert total IgE og spesifikk IgE i serum mot luftvei- og matvareallergener, og hudprikktest mot luftvei- og matvareallergener. Alle skal fylle ut spørreskjema for gradering og diagnostisering av deres mage-tarm plager.

Mulige fordeler og ulemper

Det er ingen risiko, ulemper eller ubehag ved å delta. Det eneste ubehaget kan være stikket for å ta blodprøve. Ellers opplever pasientene vanligvis ikke ubehag når man utfører hudprikktest.

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Blodprøvene for rutine "allergi screening" (total IgE, spesifikk IgE for luftvei- og matvare allergener) fra alle pasienter sendes rutine til LKB (Laboratoriet for Klinisk Biokjemi) ved Haukeland Universitetssykehus (HUS) i samme dag som de har levert blodprøve.

Det er kun autorisert personell (undertegnede) knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte:

Overlege, dr. med. Gülen Arslan Lied, Seksjon for Klinisk Spesialallergologi, Yrkesmedisin, HUS og Seksjon for Fordøyelsessykdommer, Haukeland Universitetssykehus. Telefon: 55972130

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltakelse: Alle pasienter (i løpet av ett år) som er henvist til Seksjon for Spesialallergologi, Yrkesmedisin, HUS på grunn av mistanke om allergisk sykdom med og uten mage-tarm plager skal bli inkludert i studien.

Bakgrunnsinformasjon om studien: Dette er en studie som man ønsker primært å undersøke om det er noen sammenheng mellom serum total IgE nivå inkludert serum spesifikk-IgE og hudprikktest og gastrointestinale plager, og å se dens relasjon med pollensesongen for å identifisere atopien rolle ved utvikling av mat-relaterte magetarm plager. Det er også interessant å se hvor mye atopi, tendens til allergiske sykdommer og mage-tarm plager som den generelle befolkningen har.

Undersøkelser, blodprøver og annet: Alle pasienter og kontrollgruppe skal delta i "allergologiske screening" inkludert total IgE og spesifikk IgE i serum mot luftvei- og matvareallergener, og hudprikktest mot luftvei- og matvareallergener. Alle skal fylle ut to spørreskjema for gradering og diagnostisering av deres mage-tarm plager.

Tidsskjema: Studien skal utføres ila ett år, fra høst 2011 til høst 2012.

Mulige fordeler: Fordeler er at resultatene kan være hjelpsom når vi behandler og informerer disse pasientene om sykdommen. De kan ha forståelse hvorfor plagene øker i bestemt perioder (for eksempel pollensesongen). På denne måten kan vi også se hvor mye atopi og tendens til allergiske sykdommer som den generelle befolkningen har. Vår kunnskap om mekanismen hvorfor disse pasienter har mage-tarm plager og hvordan atopi kan påvirke øker.

Mulige bivirkninger: Det er ingen ulempe eller bivirkninger ved å delta i studien. Det kan kun være ubehagelig å gi blodprøve som vanlig.

Pasientens/studiedeltakerens ansvar: Pasienten/studiedeltakeren eller verge vil bli orientert så raskt som mulig dersom ny informasjon blir tilgjengelig som kan påvirke pasientens/deltakerens villighet til å delta i studien. Pasienten/studiedeltakeren skal opplyses om mulige beslutninger/situasjoner som gjør at deres deltagelse i studien kan bli avsluttet tidligere enn planlagt.

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er: Alder, kjønn, etniske rase, blodprøve svar (Serum total IgE, spesifikk IgE mot luftvei- og matvareallergener), funn fra hudprikktest og svar fra spørreskjemaene om dine mage-tarm plager. Alt skal registreres i database (passord beskyttet). Kun undertegnede skal ha tilgang til databasen.

Biobank: Ingen

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Studien blir finansiert gjennom forskningsmidler fra Universitets i Bergen, Institutt for indremedisin.

Forsikring
Etter å ha snakket med advokat Sørli, legemiddel ansvarsforsikringen, skulle det ikke være nødvendig så lenge man ikke tester effekt av medisiner.

Informasjon om utfallet av studien
Pasientene kan få informasjon om både resultater av egen prøver og resultater av hele studien.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Stedfortredende samtykke når berettiget, enten i tillegg til personen selv eller istedenfor

(Signert av nærstående, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

SPØRRESKJEMA FOR PASIENT *(Kane, Am J Gastroenterol 2003)*

FYLT UT DATO: …………………….. TLF NUMMER:……………………………
NAVN: ……………………………… FØDSELSNR: ……………………………..

* Har du mage-tarm plager ? Yes No (sett ring rundt svaret)

1. *IBS-KRITERIER* (Sett ring rundt svaret)

Spørsmål	Svar	
1.1 Har du vært plaget av smerter eller ubehag i magen de siste 3 måneder?	Ja	Nei
1.2 Har du kjent disse plagene minst 1 dag/uke i 3 uker eller mer, i løpet av siste 3 måneder?	Ja	Nei
1.3 Er avføringen uregelmessig?	Ja	Nei
1.4 Har du mye luft i magen?	Ja	Nei
1.5 Blir smertene/ubehaget i magen bedre etter at du har hatt avføring/fått tømt deg?	Ja	Nei

2. *IBS KRITERIER SOM GIR STØTTE FOR DIAGNOSEN* (Sett ring rundt svaret)

Spørsmål	Svar	
2.1 Hvis du har diaré, hender det at avføringen er fast inn i mellom?	Ja	Nei
2.2 Hvis du har forstoppelse, hender det at avføringen er løs inn i mellom?	Ja	Nei
2.3 Har du avføring om natta?	Ja	Nei
2.4 Hva har du mest av?	Diaré	
	Forstoppelse	

3. *KVANTITERING AV IBS SYMPTOMER*
   Angis på en skala fra 0 til 10, der 0 = ingen symptomer og 10 = alvorlige symptomer
   (Kane, Am J Gastroenterol 2003)

(Angi med tall fra 0 til 10)

Spørsmål	Svar
3.1 Kvalme	
3.2 Oppblåsthet	
3.3 Magesmerter	
3.4 Forstoppelse	
3.5 Diaré	
3.6 Anoreksi (ulyst på mat)	

4. *SYMPTOMER SOM KREVER NÆRMERE VURDERING* (Sett ring rundt svaret)

Spørsmål	Svar	
4.1 Har du gått ned i vekt det siste året?	Ja	Nei
4.2 Har du sett blod i avføringen?	Ja	Nei
4.3 Har du brukt antibiotika det siste året?	Ja	Nei
4.4 Er det noen i din nærmeste familie som har eller har hatt kreft i tykktarmen? (Som nærmeste familie menes foreldre, søsken og barn.)	Ja	Nei

5. *FUNKSJONELL DYSPEPSI*   (Sett ring rundt svaret)

Spørsmål	Svar	
5.1 Har du hatt smerter eller ubehag ovenfor navlen?	Ja	Nei
5.2 Har du kjent disse plagene høyt oppe i magen minst 1 dag/uke i 3 uker eller mer, i løpet av de siste 3 måneder?	Ja	Nei
5.3 Blir smertene/ubehaget i øvre del av magen bedre etter at du har hatt avføring?	Ja	Nei

6. *HALSBRANN*   (Sett ring rundt svaret)

Spørsmål	Svar	
6.1 Har du hatt halsbrann eller sviende/brennende smerte bak brystbenet?	Ja	Nei
6.2 Har du kjent disse plagene minst 1 dag/uke i 3 uker eller mer, i løpet av de siste 3 måneder?	Ja	Nei

7. *TILLEGGSPØRSMÅL FOR Å KARAKTERISERE ALLE PASIENTENE*

(Sett ring rundt svaret)

Spørsmål	Svar	
7.1 Har du hatt mageplagene lenger enn ett år?	Ja	Nei
7.2 Har du oppsøkt lege for slike mageplager tidligere?	Ja	Nei
7.3 Mener du at stress eller psykiske faktorer betyr noe for plagene dine?	Ja	Nei
7.4 Er du engstelig for om plagene kan skyldes kreft eller annen alvorlig sykdom?	Ja	Nei

GRADERING AV MAGEPLAGER

(Aliment Pharmacol Ther 1997; 11: 395-402)

Ikke fyll ut feltene under:

1. **a)** *Er du for tiden plaget med magesmerter?*

JA   NEI

Sett kryss over Ja eller Nei

b) *Hvis ja, hvor alvorlige er disse magesmertene?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% ├──────────────────────────────┤ 100%

| Ingen smerte | Mindre alvorlig | Ganske alvorlig | Alvorlig | Svært alvorlig |

c) *Anslå antall dager du har smertene i løpet av en 10 dagers periode*
Eksempel: 4 betyr at du har vondt i magen i 4 av 10 dager.
Har du vondt i magen hver dag, skriver du 10.

Antall dager med smerte: [   ]   x 10

2. **a)** *Er du for tiden plaget med oppblåsthet eller stinnhet i magen (som du ikke forbinder med menstruasjon)?*

JA   NEI

Sett kryss over Ja eller Nei

b) *Hvis ja, hvor alvorlig er denne oppblåstheten/stinnheten?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% ├──────────────────────────────┤ 100%

| Ingen oppblåsthet | Mindre alvorlig | Ganske alvorlig | Alvorlig | Svært alvorlig |

3. *Hvor fornøyd er du med avføringsmønsteret ditt?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% ├──────────────────────────────┤ 100%

| Svært fornøyd | Ganske fornøyd | Lite fornøyd | Svært lite fornøyd |

4. *I hvor stor grad føler du at mageplagene dine påvirker eller forstyrrer livet ditt?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% ├──────────────────────────────┤ 100%

| Ikke i det hele tatt | Ikke særlig mye | Ganske mye | Fullstendig |

Sum

Table 1 and table 2 present overview of patients from patient subgroups and total patient group with elevated levels of specific IgE (> 0.35 kU/L) to inhalant or food allergens.

Table 1: Prevalence of IgE sensitization to inhalant allergens[*] in patients.

Allergen	Patients with GI complaints (n =81)		Patients with other complaints (n = 80)		Patient group (n = 161)	
	%	n	%	n	%	n
Dermatophagoides pteronyssinus	33.3	27	41.3	33	37.3	60
Timothy	42.0	34	50.0	40	46.0	74
Mugwort	22.2	18	16.2	13	19.3	31
Cat	25.9	21	28.8	23	27.3	44
Dog	35.8	29	40.0	32	37.9	61
Horse	19.8	16	20.0	16	19.9	32
Birch	39.5	32	40.9	32	39.8	65
Cladosporium herbarum	3.7	3	7.5	6	5.6	9

[*] Standard panels of inhalant (Phadiatop) allergens (ImmunoCAP, Phadia AB, Uppsala, Sweden).

Table 2: Prevalence of IgE sensitization to food allergens[*] in patients.

Allergen	Patients with GI complaints (n = 81)		Patients with other complaints (n = 80)		Patient group (n = 161)	
	%	n	%	n	%	n
Wheat	13.6	11	20.0	16	15.5	25
Cow's milk	6.2	5	10.0	8	8.1	13
Egg white	6.2	5	8.8	7	7.5	12
Cod	0	0	3.8	3	1.9	3
Soy bean	8.6	7	15.0	12	11.8	19
Peanut	12.4	10	13.2	14	14.9	24
Hazelnut	17.3	14	26.3	21	21.7	35
Rye	9.9	8	7.5	6	8.7	14
Barley	13.6	11	6.3	5	9.9	16
Oats	7.4	6	6.3	5	6.8	11

[*] Standard panels of food (fx5) allergens (ImmunoCAP, Phadia AB, Uppsala, Sweden).

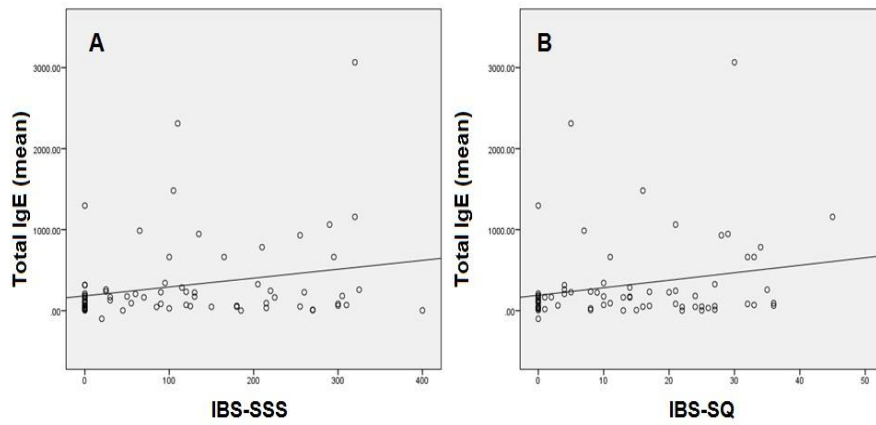*Correlation analysis in patient subgroup with other complaints*

In our patient subgroup with GI complaints as primary cause of reference, total IgE was not significantly correlated with IBS-SSS (r = -.034, p = .772) or IBS-SQ (r = -.046, p = .687) (Figure 1, A and B).
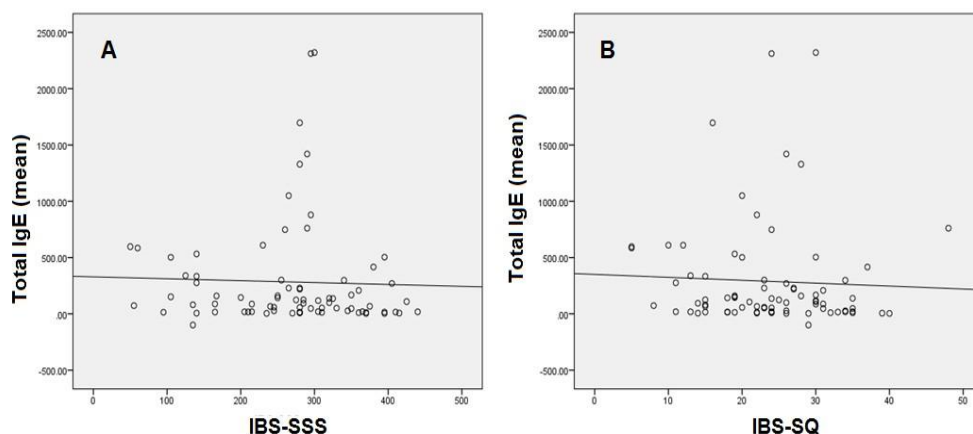
Figure 1: Correlation analysis in patient subgroup with GI complaints between A: total IgE and IBS-SSS (r = -.034, p = .772) and B: total IgE and IBS-SQ (r = -.046, p = .687)

Correlation analysis in patient subgroup with other complaints

In our patient subgroup with other complaints as primary cause of reference, the results were somewhat different, whereas total IgE significantly correlated with IBS-SSS (r = .241, p = .037), but not IBS-SQ (r = .217, p = .067) (Figure II, A and B).

Figure II: Correlation analysis in patient subgroup with other complaints between: total IgE and IBS-SSS (r = .241, p = .037) and B: total IgE and IBS-SQ (r = .217, p = .067).

Patient subgroup with GI complaints

In patient subgroup with GI complaints as primary cause of reference, no significant difference in GI complaints was observed between atopic and non-atopic patients. On average, non-atopic patients reported more GI complaints (mean IBS-SSS = 284.09) than atopic (mean IBS-SSS = 255.05). However, this difference was not statistically significant (p = .184). This was also true when comparing IBS-SQ means, whereas non-atopic reported more GI complaints (mean IBS-SQ = 24.61) than atopic (mean IBS-SQ = 23.11), (p = .444).
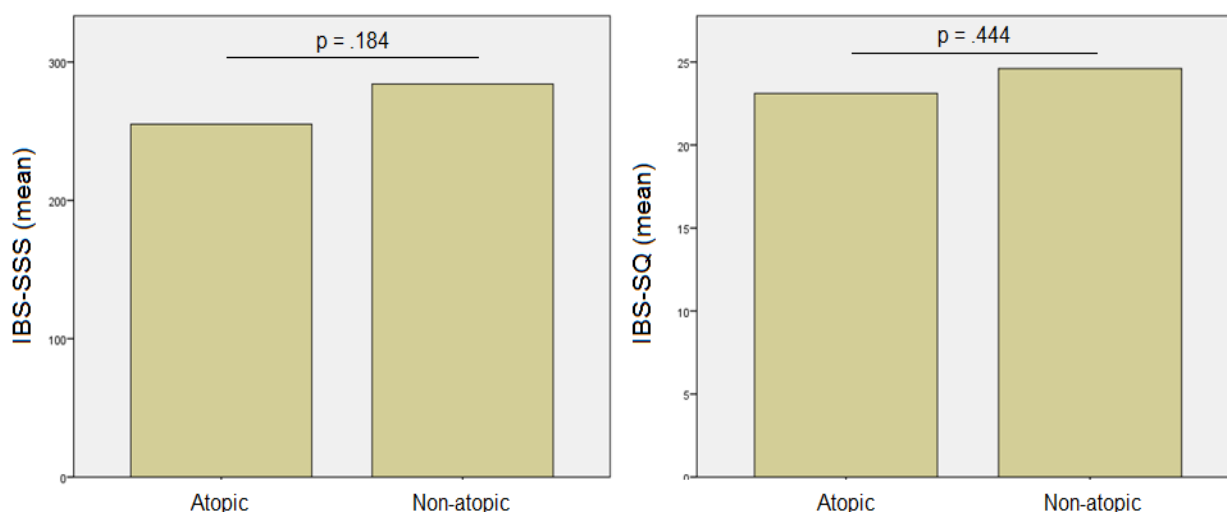
Figure III: Mean IBS-SSS score (left) and mean IBS-SQ score (right) between atopic and non-atopic in patient subgroup with GI complaints as primary cause of reference.

Patient subgroup with other complaints

In the patient subgroup with other allergic symptoms as primary cause of reference, the results was somewhat different, where atopic patients on average reported more GI complaints (mean IBS-SSS: 117.79) than non-atopic (mean IBS-SSS: 111.79) (p = .861) when comparing IBS-SSS scores, whereas non-atopic on average reported more GI complaints (mean IBS-SQ: 14.64) than atopic (mean IBS-SQ: 13.84) (p = .845) when comparing scores from the IBS-SQ scheme. However, neither of the differences in scores were significant.
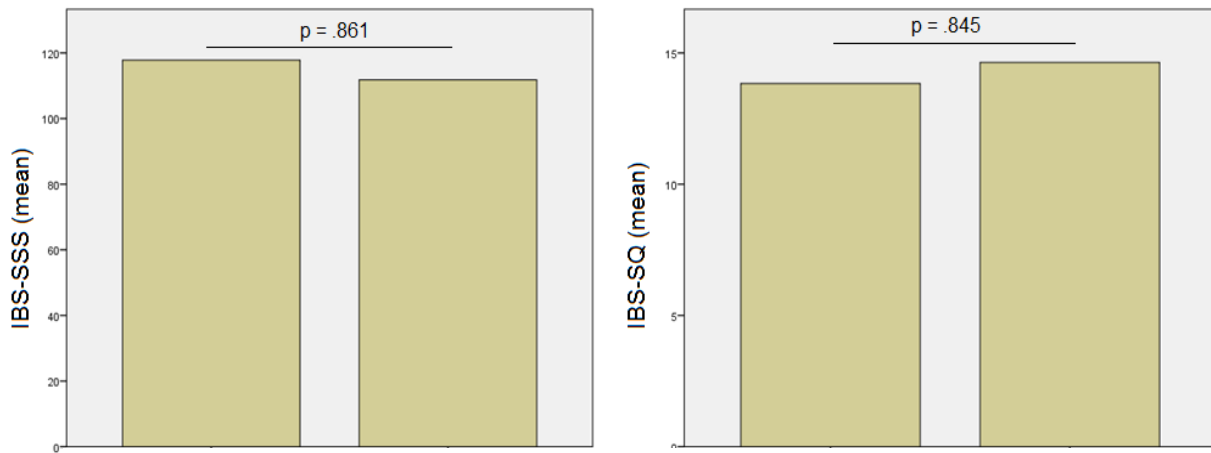
Figure IV: Mean IBS-SSS score (left) and mean IBS-SQ score (right) between atopic and non-atopic in patient subgroup with other complaints as primary cause of reference.

Linear multivariate regression analyzes including IBS-SQ as description of GI complaints are presented in the following tables.

Patient group

Table III: Multiple regression analysis with GI complaints (IBS-SQ) as dependent variable and total IgE, sex, age and atopic sensitization as independent variables in patient group. Model 1 is unadjusted and model 2 is adjusted for atopic sensitization, sex and age.

	IBS-SQ			
	B	95 % CI	SE b	p-value
Model 1 (unadjusted)				
Total IgE	.002	(-.002, .006)	.002	.311
Model 2				
Total IgE	.003	(-.001, .007)	.002	.110
Atopic sensitization*	-5.051	(-9.306, -.796)	2.152	**.020**
Sex	-3.035	(-7.026, .955)	2.019	.135
Age	-.133	(-.260, -.007)	.064	**.039**

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .007 for model 1, ΔR^2 = .076 for step model 2 (p = .014).
*Atopy was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) and/or standard panels of food allergens (fx5).

General population

Table IV: Multiple regression analysis with GI complaints (IBS-SQ) as dependent variable and total IgE, sex, age and atopic sensitization as independent variables in general population group. Model 1 is unadjusted and model 2 is adjusted for atopic sensitization, sex and age.

	IBS-SQ			
	b	(95% CI)	SE b	p-value
Model 1 (unadjusted)				
Total IgE	.002	(-.001, .004)	.001	.201
Model 2				
Total IgE	.003	(.000, .005)	.001	.057
Atopic sensitization*	-1.385	(-3.033, .263)	.839	.099
Sex	-1.142	(-2.448, .165)	.665	.087
Age	-.044	(-.141, .054)	.050	.381

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .004 for step 1, ΔR^2 = .014 for step 2 (p = .079).
*Atopy was defined as having elevated specific IgE (> 0.35kU/L) to one of the following allergens: grass, cat or *Dermatophagoides pteronyssinus*.

Total study population

Table V: Multiple regression analysis of GI complaints (IBS-SQ) as dependent variable and total IgE, sex, age and atopic sensitization as independent variables in total study population (n = 639). Model 1 is unadjusted, and model 2 is adjusted for atopic sensitization, sex, age, atopic and group sample.

	IBS-SQ			
	b	95% CI	SE b	p-value
Model 1				
Total IgE	0.06	(.004, .009)	.001	**<.001**
Model 2				
Total IgE	.003	(.000, .005)	.001	**.005**
Atopic sensitization*	-2.734	(-4.356, -1.112)	.826	**.001**
Sex	-1.559	(-2.912, -.207)	.689	**.024**
Age	-.086	(-.158, -.015)	.036	**.018**
Patient group or general population group	12.014	(9.943, 14.084)	1.054	**<.001**

The following symbols represent: b = unstandardized beta coefficient and SE = standard error.
Note: R^2 = .046 for model 1, ΔR^2 = .293 for model 2 (p < .001).
*Atopic sensitization was defined as having elevated specific IgE (> 0.35kU/L) to standard panels of inhalant allergens (phadiatop) in patient group and as having elevated specific IgE (> 0.35kU/L) to grass, cat or *Dermatophagoides pteronyssinus* in general population group.