

ORIGINAL ARTICLE

Neither self-reported atopy nor IgE-mediated allergy are linked to gastrointestinal symptoms in patients with irritable bowel syndrome

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Abstract

Background: Among patients with irritable bowel syndrome (IBS), atopic disease has been proposed as a common comorbidity increasing the IBS symptom burden. We therefore assessed the prevalence of self-reported atopy among patients with IBS as compared to non-IBS controls, and whether atopy and higher serum IgE levels were associated with increased IBS symptom severity.

Methods: Levels of total and specific IgE in serum were measured and questionnaires assessing the presence of atopic disease (ie, eczema, asthma, rhinoconjunctivitis, and pollen allergy), gastrointestinal symptom burden, food intolerance, somatic, and psychological symptoms were completed.

Key results: In total, 223 patients with IBS and 47 controls participated. Presence of atopic disease was reported in 55% of patients with IBS compared to 40% of controls ($P = .07$). IBS patients with atopic manifestations ($N = 123$) had higher total serum IgE levels (median 31 vs 16 kU_A/L, $P < .001$) and higher prevalence of self-reported food intolerance (28% vs 9%, $P = .002$) than non-atopic IBS patients ($N = 100$), respectively, but no major difference in gastrointestinal or psychological symptom burden was noted. However, severe somatic symptoms were more common among atopic than non-atopic patients with IBS (38% vs 27%, $P = .028$). We found no associations between self-reported atopy and IBS symptom severity using linear regression models.

Conclusions & Inferences: Atopic disease is common in patients with IBS, but that is also true for subjects without IBS. The presence of atopic disease in IBS is associated with self-reported food intolerance and somatic symptom severity, but unrelated to IBS symptom severity.

KEYWORDS

atopic disease, IgE, irritable bowel syndrome, self-perceived food intolerance

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, affecting approximately 11% of the adult population.¹

The disease is characterized by recurrent abdominal pain and altered bowel habits, ie, a change in the frequency and/or appearance of stools.² A range of other gastrointestinal (GI) and non-GI symptoms are often concurrently present in patients with IBS,

such as dyspepsia, migraine, headaches, fibromyalgia, interstitial cystitis, and dyspareunia.^{3–5} These comorbidities may share some pathophysiologic traits with IBS, such as visceral hypersensitivity, a sustained immune activation after infection, disturbances in the gut-brain axis communication, altered gut microbiota composition, and psychiatric distress.²

Atopic disease has further been identified as a comorbid condition with symptoms that overlap with IBS.⁶ Atopy is defined as having a hereditary predisposition to develop classic allergic diseases: atopic dermatitis, allergic rhinitis, and asthma. It also involves the ability to produce IgE in response to common allergens, such as dust mite, grass pollen, and food allergens. Mast cells have a primary role in atopic disease and release inflammatory mediators, eg, cytokines, histamine, and proteases, when cell-bound IgE are cross-linked by allergens. Various studies suggest that allergen exposure, whether ingested or inhaled, may lead to IBS manifestations in atopic individuals.^{7–9}

Symptoms of IBS are often reported to be provoked by food intake^{10,11} and a large share of patients with IBS report food intolerance of some degree.¹² The mechanisms of food intolerance are largely unknown, but studies suggest that type 1 hypersensitivity reactions (IgE-mediated) may be accountable for symptom generation in a subgroup of IBS patients.¹³ Several research groups have reported increased numbers of mucosal mast cells, within proximity to nerve endings, in IBS patients.^{14,15} Furthermore, increased numbers of mast cells have been suggested to be linked to increased colonic permeability, abdominal pain perception, and rectal sensitivity in this patient group.^{14,16} Thus, the increased presence and activity of mucosal mast cells in atopic disease and IBS proposes a link between these disorders, and may therefore play a unique role in a subgroup of IBS patients.

The presence of allergy has been suggested to correlate with more severe IBS symptoms¹⁷ and atopic IBS has been proposed as a new IBS subgroup with allergic manifestations.¹⁸ Still, few studies on this potentially new subgroup exist and whether IBS patients with atopic manifestations differ from non-atopic IBS patients, with regard to IBS symptom burden and severity, remain to be established. In this study, we hypothesized that the presence of atopic manifestations is common among patients with IBS, and that self-reported atopy and food intolerance are linked to increased IBS symptom burden. We therefore assessed (i) if the prevalence of atopic disease is higher among individuals with IBS than in control subjects, (ii) if the severity and pattern of symptoms differ between atopic and non-atopic IBS patients, and (iii) if the presence of atopic disease is associated with GI complaints in patients with IBS.

2 | MATERIALS AND METHODS

2.1 | Study population

We included patients with IBS according to the ROME III criteria¹⁹ who participated in studies at our specialized unit for functional GI

Key Points

- Atopic disease is common in the general population and has been suggested to be associated with IBS, leading to more severe IBS symptoms.
- Atopic disease was common in IBS, but not more frequent than in control subjects. IBS patients with atopic disease reported food intolerance and severe somatic symptoms more frequently, but not more severe IBS symptoms than IBS patients without atopy.
- Atopy in IBS may explain a minor part of the symptomatology and food-related symptoms, but are not associated with IBS symptoms per se.

disorders at Sahlgrenska University Hospital, Gothenburg, Sweden. These studies aimed at characterizing pathophysiologic traits of IBS with regard to gut permeability, oro-anal transit time, visceral hypersensitivity and inflammatory markers, and patients and control subjects were enrolled consecutively during 2012–2014. Patients were excluded from participation if other diagnoses could explain their GI symptoms, if they had severe psychiatric or chronic illnesses, or was pregnant. Demographic and disease-related factors were assessed during a structured interview and patients completed self-administered questionnaires (see below). Also, 47 controls who perceived themselves as healthy were consecutively recruited through advertisement in the local newspaper. The control subjects were screened and excluded if they showed signs of GI symptoms or had any severe chronic illnesses, except for atopic disease. These studies were performed after receiving verbal and written informed consent from all study participants and the study was approved by the Regional Ethical Review Board in Gothenburg (dnr 489-02, 731-09).

2.2 | Total and specific serum IgE and eosinophilic granulocytes

Blood samples were obtained from all study subjects. Levels of IgE and eosinophils were measured at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden. To screen for allergy, ImmunoCAP Phadiatop (PHADIA AB, Uppsala, Sweden) was used for inhaled allergens (birch, timothy, mite (*D. pteronyssinus* and/or *D. farinae*), mugwort, cat, dog, horse), and fx5 ImmunoCAP mixed food plate (PHADIA AB) for ingested allergens (fish, peanut, milk, egg, soybean, wheat). When these tests were positive, quantification of specific IgE antibodies targeting a single allergen was performed by use of monospecific ImmunoCaps. Increased level of total IgE was defined as a concentration of more than 120 kU_A/L, and increased levels of specific IgE was defined as a concentration of 0.35 kU_A/L or more. The number of eosinophilic granulocytes in peripheral blood was determined by automated cell

counting (Sysmex Corporation, Kobe, Japan). Eosinophilia was defined as a concentration of $0.4 \times 10^9/L$ or more based on normal values at the local chemistry laboratory.

2.3 | Questionnaires

All participants completed the following questionnaires:

2.3.1 | Self-reported atopic disease

This questionnaire has been developed at the Department of Allergology at Sahlgrenska University Hospital, Gothenburg, Sweden, with the aim to evaluate the presence of atopic manifestations such as eczema, asthma, and/or rhinoconjunctivitis (both present manifestations and childhood manifestations). It also covers aspects of food allergy and intolerance (where respondents answer if they perceive themselves as having a food allergy or intolerance with "yes" or "no", and this question is not specifically related to GI symptoms), pollen allergy, family history of allergies, smoking habits, and triggering factors for atopic manifestations. In this paper, we use the presence of atopic manifestations in childhood to define atopic disease and having self-reported food allergy/intolerance if respondents state that they perceive themselves as having a food allergy or intolerance.

2.3.2 | Food-related adverse GI reactions

This questionnaire was used to assess adverse reactions after intake of food.¹⁰ It comprises 56 different food items or food groups, which are grouped according to potential symptom generating mechanism, or by their contents (eg, foods containing incompletely absorbed carbohydrates, fat, biogenic amines, lectins, preservatives, histamine-releasing agents, or agents causing cross-reactions with airborne allergens). The food groups were chosen for their reported validity to induce food intolerance and allergy.²⁰⁻²² For the purpose of this study, only food items reported to cause GI symptoms (irrespective of type) were included in the analyses. The results were used to assess the proportion of subjects reporting GI symptoms after food intake and the number of food items reported to cause GI symptoms in each individual as a measure of the degree of self-reported food intolerance.¹⁰ The questionnaire has not been formally validated, but is used as a clinical tool to evaluate food-related intolerance and allergy.

2.3.3 | Hospital anxiety and depression (HAD) scale

The HAD scale is an instrument designed for measuring symptoms of anxiety and depression in subjects attending an outpatient medical clinic.²³ The scores are not affected by bodily illness. The scale consists of 14 items, each using a 4-point Likert scale (0-3) with subscales for anxiety (7 items) and depression (7 items), which provides a score between 0 and 21 points on each sub-scale. The higher the score, the more pronounced the symptoms. A score of 7 or less

denote a non-case, 8-10 points a doubtful case and 11 points or more a definite case of anxiety or depression. A score of 11 or more was used as a cutoff to define presence of anxiety and depression in this study.

2.3.4 | The Patient Health Questionnaire (PHQ-15)

The PHQ-15 is a questionnaire used for assessment of somatic symptom severity.²⁴ The questionnaire inquires 15 different symptoms or symptom clusters (mental, physical, social, general and pain) that account for more than 90% of the physical complaints (excluding upper respiratory tract symptoms) reported in the outpatient setting. Each symptom is scored from 0 ("not bothered at all") to 2 ("bothered a lot"), and scores of 5, 10, and 15 has been used to represent cutoff points for low, medium, and high somatic symptom severity, respectively.²⁴ In the regression analysis, the scores were used as continuous variables.

Participants with IBS also completed the following questionnaires:

2.3.5 | IBS severity scoring system (IBS-SSS)

The IBS severity scoring system (IBS-SSS) is a questionnaire commonly used to evaluate the severity of IBS symptoms.²⁵ Five questions are included in an overall IBS severity score: abdominal pain severity, abdominal distension severity, dissatisfaction with bowel habits, and influence of IBS on life in general are rated with visual analog scales (VAS) (0-100 points each), and abdominal pain frequency is defined as the number of days with pain during the last 10 days (days with pain multiplied with 10, ie, 0-100 points). Patients with IBS-SSS < 175 are defined as mild IBS, 175-300 as moderate IBS, and >300 as severe IBS.²⁵

2.3.6 | Irritable bowel syndrome of quality of life (IBSQOL)

The Irritable Bowel Syndrome Quality of Life Questionnaire (IBSQOL) is a disease-specific questionnaire to measure effects of IBS symptoms on quality of life.²⁶ This scale is divided into 9 dimensions: emotional functioning, mental health, physical functioning, energy, sleep, food/diet, social role, physical role, and sexual relations. The summed total score ranges from 0 to 100, where a low score implies poor quality of life.

2.4 | Statistical analysis

Demographic and clinical data are presented as proportions for categorical variables and as mean $\pm$ standard deviation (SD) for continuous, normally distributed variables, and median with interquartile range (IQR) for continuous variables with skewed distributions. Comparisons between groups were performed using independent samples t-test for equal means for continuous, normally distributed variables; Mann-Whitney U test for non-normally distributed variables; and χ^2 -test or Fisher's exact

test for categorical variables. Comparisons of means between more than 2 groups were performed by analysis of variance. Two-tailed P -values $< .05$ were considered statistically significant. Furthermore, logistic regression analysis was used to identify predictors of atopic disease in IBS patients, with self-reported atopy as a dichotomous dependent variable (0 = no atopic disease, 1 = having atopic disease). Also, in line with our hypotheses, linear regression analysis was used to evaluate any associations between atopic disease and IBS symptoms (IBS-SSS) among IBS patients. First, simple linear regression analysis was performed to investigate any effect of each independent variable, based on a priori decision: gender, age, somatic symptoms (PHQ-15), total IgE levels, eosinophil counts, self-reported food allergy/intolerance (yes/no), and number of food items causing adverse reactions. Thereafter,

these variables were modeled in a hierarchical multiple regression analysis as follows: (i) demographic variables (gender and age), (ii) non-immunological covariates (somatic symptoms) and finally, (iii) allergy-related covariates (total IgE levels, eosinophil counts, self-reported food allergy/intolerance, and number of food items causing adverse reactions). Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0.0 (Armonk, NY: IBM Corp.).

3 | RESULTS

In total, 223 patients with IBS and 47 control subjects were included. Of all participants who reported having had any atopic condition in

TABLE 1 Prevalence of atopic manifestations, extra intestinal symptoms, presence of food-related hypersensitivity, and total and specific IgE to common inhalant and food allergens among patients with IBS and non-IBS controls

	Patients with IBS N = 223	Non-IBS controls N = 47	P value
Age, y (median (range))	31 (18-72)	27 (19-53)	.049
HAD anxiety (mean $\pm$ SD)	8.5 $\pm$ 4.6	4.6 $\pm$ 3.1	<.001
HAD depression (mean $\pm$ SD)	5.1 $\pm$ 3.6	2.5 $\pm$ 2.4	<.001
PHQ-15 (mean $\pm$ SD)	12.8 $\pm$ 4.7	3.3 $\pm$ 2.2	<.001
Number of food items causing GI symptoms (median (IQR))	6 (10)	0 (0)	<.001
Total IgE kU _A /L (median (IQR))	21.0 (51)	27.0 (68)	.09
	N (%)	N (%)	P value
Gender: women	164 (74)	29 (62)	.10
Self-reported food intolerance: yes	43 (19)	3 (6)	.025
Any atopic manifestation	123 (55)	19 (40)	.07
Eczema	69 (31)	10 (21)	.019
Asthma	40 (18)	4 (9)	.19
Rhinoconjunctivitis	48 (22)	6 (13)	.19
Pollen allergy	66 (31)	11 (23)	.48
Elevated total IgE > 120 kU _A /L	33 (15)	9 (19)	.51
Increased blood eosinophils: yes	11 (5)	1 (2)	.70
Positive phadiatop test ^a	72 (32)	16 (34)	.82
Birch	37 (17)	10 (21)	.53
Timothy	37 (17)	10 (21)	.44
Mite	23 (10)	9 (19)	.13
Mugwort	7 (3)	7 (15)	.004
Positive mixed food plate (fx5) ^b	4 (2)	3 (6)	.10
Peanuts	3 (1)	3 (6)	.07
Wheat	3 (1)	3 (6)	.07
Milk	2 (1)	1 (2)	.44
Soybean	1 (0.5)	3 (6)	.018
Egg	1 (0.5)	1 (2)	.32

IBS: irritable bowel syndrome; IQR: interquartile range; IgE: immunoglobulin E; PHQ: The Patient Health Questionnaire; HAD: Hospital Anxiety and depression Scale.

^aScreening for inhalant allergens.

^bScreening for ingested allergens (fish, peanut, milk, egg, soybean, wheat).

TABLE 2 Demographic characteristics, extraintestinal symptoms, and IBS subtype in patients with irritable bowel syndrome with or without atopy

	Atopic patients ^a N = 123	Non-atopic patients N = 100	P value
	Mean±SD	Mean±SD	
Age, y ^b	30 (18-66)	34 (19-72)	.09
BMI, kg/m ²	23.1 ± 3.6	23.3 ± 3.9	.70
HAD anxiety	8.3 ± 4.6	8.7 ± 4.6	.47
HAD depression	4.9 ± 3.3	5.4 ± 4.0	.32
IBSQOL	555 ± 167	548 ± 169	.80
PHQ-15	13.5 ± 4.7	12.1 ± 4.6	.030
	N (%)	N (%)	P value
Gender: women	98 (80)	66 (66)	.021
IBS subtype (%)			
IBS-D	20 (17)	21 (22)	.60
IBS-C	11 (9)	7 (7)	
IBS-M	75 (62)	61 (63)	
IBS-U	14 (12)	8 (8)	

IBS: irritable bowel syndrome; BMI: Body Mass Index; HAD: Hospital Anxiety and depression Scale; IBSQOL: IBS quality of life; PHQ: The Patient Health Questionnaire; IBS-D: IBS with diarrhea; IBS-C: IBS with constipation; IBS-M: mixed IBS; IBS-U: unsubtyped IBS.

^aSelf-reported history of rhinoconjunctivitis, pollen allergy, eczema, or asthma.

^bMedian (range).

childhood (N = 142), 83.9% reported having atopic symptoms also later in life.

3.1 | IBS patients vs non-IBS controls

The gender distribution was similar in the 2 study groups, with 74% women among IBS patients and 62% women among controls ($P = .10$). However, IBS patients were older than controls; median age 31 and 27 years, respectively ($P = .049$). As for the questionnaire data, IBS patients had more severe anxiety and depression (HAD), and more somatic symptoms (PHQ-15) than controls, ($P < .001$ for all) (Table 1).

Compared to controls, there was a trend for IBS patients to report atopic manifestations more frequently (55% vs 40%, $P = .07$), and among them a significantly higher prevalence of eczema (31% vs 21%, respectively, $P = .019$) (Table 1). IBS patients also reported food allergy/intolerance (not specified as related to GI symptoms or not) more frequently than controls (19% vs 6%, $P = .025$).

In all, 193 IBS patients (87%) reported having GI symptoms after intake of at least one of the food items surveyed, whereas only 10 controls (22%) reported having GI symptoms after at least 1 food item, with a higher number of food items causing symptoms in patients with IBS ($P < .001$). However, no difference in total serum IgE

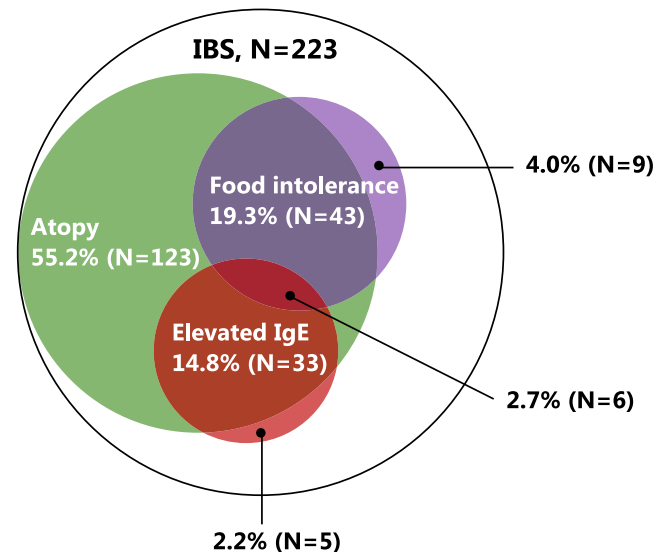


FIGURE 1 The overlap between atopy, food intolerance and elevated IgE levels in patients with IBS. Of all 223 IBS patients, 55.2% (N = 123) had atopic disease, 19.3% (N = 43) reported food allergy/intolerance, and 14.8% (N = 33) had elevated total IgE levels. A total of 38.1% (N = 85) did not have/report any of these, while 2.7% (N = 6) had all 3 combined

or blood eosinophil counts was noted between IBS patients and controls. Furthermore, screening for common inhalant allergens was positive in 32% of IBS patients and 34% of controls, where specific IgE to birch, timothy and mite were most prevalent, with no differences between patients with IBS and controls. Specific IgE to food allergens was rare in both groups and with no difference between groups, Table 1.

3.2 | IBS patients—atopic vs non-atopic

Demographic and disease-related characteristics among atopic IBS patients, ie, those who have reported any atopic manifestations during childhood (N = 123) and IBS patients without atopic manifestations (N = 100) are presented in Table 2. The proportion of women was higher among atopic IBS patients than among non-atopic IBS patients (80% vs 66%, $P = .021$). The distribution of IBS subgroups was similar between atopic and non-atopic patients. No difference in the prevalence of anxiety or depression, or in any of the IBSQOL domains could be noted between the groups. However, atopic patients scored higher in PHQ-15 than non-atopic patients ($P = .030$) and a larger proportion reported having severe somatic symptoms (38% vs 27%, $P = .028$), respectively.

The overlap of atopic disease, self-perceived food intolerance and elevated IgE levels in IBS patients can be seen in Figure 1. IBS symptom severity did not differ between atopic and non-atopic IBS patients (Table 3), and there were no significant differences in IBS-SSS between those who reported no (309 ± 87), 1 (310 ± 84), 2 (309 ± 96), or 3 (356 ± 71) of these factors (atopic disease, self-perceived food intolerance, elevated IgE levels) ($P = .66$).

TABLE 3 Factors related to allergy, food, and IBS among atopic and non-atopic patients with IBS

	Atopic IBS ^a N = 123	Non-atopic IBS N = 100	
	Mean±SD	Mean±SD	P value
IBS-SSS, total score	312.2 ± 91.0	307.3 ± 84.0	.68
Pain severity	53 ± 26	49 ± 26	.22
Pain frequency	58 ± 34	59 ± 34	.86
Bloating severity	60 ± 29	60 ± 28	.97
Bowel habit dissatisfaction	72 ± 24	70 ± 26	.49
Daily life interference	70 ± 22	71 ± 21	.79
Number of food items causing GI symptoms ^b	6.0 (10.0)	6.0 (10.8)	.63
Total IgE kU _A /L ^b	31.0 (90.0)	16.0 (23.7)	<.001
	N (%)	N (%)	P value
Self-reported food allergy/intolerance: yes	34 (28)	9 (9)	.002
Increased blood eosinophils: yes	5 (4)	6 (6)	.50
Elevated total IgE > 120 kU _A /L	28 (23)	5 (5)	<.001
Positive phadiatop test ^c	60 (49)	12 (12)	<.001
Birch	33 (27)	4 (4)	<.001
Timothy	34 (28)	3 (3)	<.001
Mite	19 (15)	4 (4)	.007
Mugwort	7 (6)	0 (0)	.018
Positive mixed food plate (fx5) ^d	6 (5)	1 (1)	.076
Peanuts	3 (2)	0 (0)	.26
Wheat	3 (2)	0 (0)	.26
Milk	2 (2)	0 (0)	.50
Soybean	1 (1)	0 (0)	1.0
Egg	1 (1)	0 (0)	1.0

IBS: irritable bowel syndrome; IBS-SSS: IBS severity scoring system; GI: gastrointestinal; IgE: Immunoglobulin E.

^aSelf-reported history of rhinoconjunctivitis, pollen allergy, eczema, or asthma.

^bMedian (interquartile range).

^cScreening for inhalant allergens.

^dScreening for ingested allergens (fish, peanut, milk, egg, soybean, wheat).

As can be expected, IBS patients with atopic disease had higher levels of total serum IgE ($P < .001$), and a higher proportion of atopic IBS patients tested positive in the screening for airborne allergens than non-atopic IBS patients ($P < .001$). However, few IBS patients, irrespective of presence or absence of atopy, tested positive in the screening for ingested allergens, with no difference between the groups (Table 3).

3.3 | Self-reported food allergy/intolerance

The prevalence of self-reported food allergy/intolerance was higher in atopic than in non-atopic IBS patients (28% vs 9%, $P = .002$). Patients who reported having food allergy/intolerance had higher anxiety (9.2 vs 7.5, $P = .029$) and depression scores (5.6 vs 4.5, $P = .049$), and more somatic symptoms (12.9 vs 10.8, $P = .023$) than patients without self-reported food allergy/intolerance. However, neither the levels of total serum IgE (23 vs 19 kU/L, $P = .96$) nor

specific IgE levels (data not shown) differed between patients with and without self-reported food intolerance.

Among atopic IBS patients, those with self-perceived food allergy/intolerance reported a higher number of food items causing GI symptoms compared to those without food intolerance (median number of food items of 10.5 and 5, respectively, $P = .043$), Figure 2. However, this did not translate into differences in IBS symptom severity, between atopic and non-atopic patients with or without food intolerance, Figure 3.

The frequency of IBS patients who reported food allergy/intolerance was similar among IBS subgroups, ie, IBS-D (12.2%), IBS-C (23.5%), IBS-M (20.6%), and IBS-U (13.6%), $P = .64$.

3.4 | Predictors for reporting atopy in IBS

Predictors for reporting atopic disease among patients with IBS are presented in Table 4. In the bivariate model, variables that

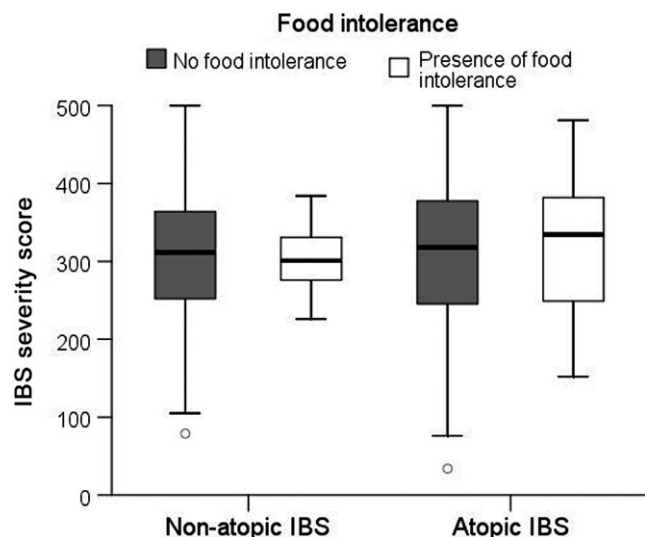


FIGURE 2 Number of food items reported to cause gastrointestinal symptoms among non-atopic and atopic patients with IBS. Atopic patients with self-reported food allergy/intolerance ($N = 36$) reported a higher number of foods causing GI symptoms than atopic patients without self-reported food allergy/intolerance ($N = 106$), $P = .043$. Box plots shows median values (solid horizontal line) 50th percentile values (box outline), 90th percentile values (whiskers) and outlier values (circles and asterisks)

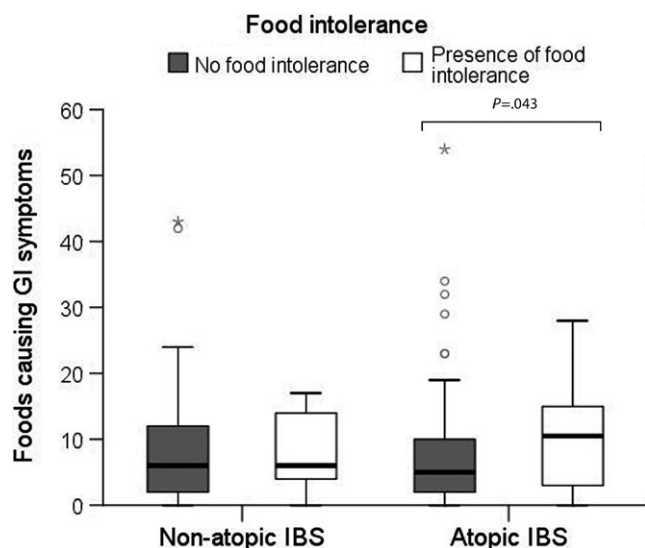


FIGURE 3 IBS symptom severity score among non-atopic and atopic patients with IBS. No difference in IBS-SSS could be seen among non-atopic and atopic IBS patients, whether or not they had reported food allergy/intolerance. Box plots shows median values (solid horizontal line) 50th percentile values (box outline), 90th percentile values (whiskers), and outlier values (circles and asterisks)

significantly increased the odds ratio (OR) for atopic disease was female gender (OR 1.73, $P = .022$), having self-reported food allergy/intolerance (OR 3.86, $P = .001$), elevated IgE levels (OR 5.60, $P = .001$), and severe somatic symptoms (OR 2.54, $P = .009$). In the

multivariable analysis, having self-reported food allergy/intolerance, elevated IgE levels and severe somatic symptoms, but not gender, remained statistically significant.

3.5 | Association between atopic disease and IBS symptom severity

In the simple linear regression analysis, having atopic manifestations was not associated with IBS symptom severity (IBS-SSS) ($P = .68$), whereas gender and somatic symptom severity were found to be significantly associated with IBS-SSS (Table 5). Having self-reported food allergy/intolerance was not significantly associated with IBS-SSS, but the number of food items reported to cause GI symptoms was significantly associated with an increase in IBS-SSS ($P < .001$).

In the first multivariable model of the association between self-reported atopy and IBS-SSS, adjusting for gender and age changed the B -coefficient from 4.96 to -0.86 and the model remained not statistically significant (Table 6). This model explained 6% of the total variation in IBS-SSS. When also adjusting for somatic symptoms in the second model, the proportion of explained variation increased to 27%. In the final full model, when also adjusting for total IgE levels, eosinophil counts, self-reported food intolerance, and the number of food items causing GI symptoms, having atopic disease was not significantly associated with IBS-SSS ($B = -8.56$, $P = .44$). The final full model explained 30% of the variation in IBS symptom severity, and variables that remained statistically significant were the severity of somatic symptoms and the number of food items reported to cause GI symptoms ($P < .001$ for both).

4 | DISCUSSION

In this study, we have demonstrated that self-reported atopic disease was common among patients with IBS, but not different from control subjects, and that neither total nor specific serum IgE levels differed between the groups. Furthermore, there was no difference in IBS symptom severity comparing atopic and non-atopic IBS patients. However, patients with IBS did report a higher prevalence of self-perceived food allergy/intolerance as compared to controls but having elevated levels of serum IgE to common ingested (or inhaled) allergens was not associated with increased IBS symptom severity. Of notice, IBS patients with atopic disease reported more severe somatic symptoms and more commonly had self-reported food allergy/intolerance than IBS patients without atopy, which might be explained by an increased tendency to report symptoms in general in these patients.

The frequency of IBS patients reporting atopic disease in this study is similar to a study performed by Lillestøl et al. where atopic disease was reported among 61% of patients with gastrointestinal complaints.²⁷ In a study by Jones et al. looking at the overlap of functional GI disorders, atopy and mood disorders, a significantly higher prevalence of atopic disease could be seen among individuals

TABLE 4 Bivariate and multivariable logistic regression of predictors for atopic IBS

	Bivariate			Multivariable		
	OR	95% CI for OR		OR	95% CI for OR	
		Lower	Upper		Lower	Upper
Gender ^a	2.019*	1.11	3.69	1.640	0.75	3.61
Age	0.980	0.96	1.00	0.983	0.96	1.01
Anxiety ^b	0.723	0.42	1.26	0.552	0.27	1.13
Depression ^b	0.517	0.18	1.51	0.575	0.14	2.33
Self-reported food intolerance ^b	3.863***	1.75	8.56	4.510**	1.76	11.58
Elevated total IgE ^b	5.600***	2.07	15.13	5.015**	1.73	14.52
Eosinophilia ^b	0.657	0.19	2.22	0.624	0.14	2.60
Number of food items causing GI symptoms	1.008	0.98	1.04	0.994	0.95	1.04
IBS-SSS						
No/mild (ref)						
Moderate	1.132	0.31	3.77	0.490	0.12	1.94
Severe	0.954	0.58	1.66	0.485	0.12	1.98
PHQ-15						
No/mild (ref)						
Moderate	1.919	0.98	3.75	1.995	0.91	4.37
Severe	2.539**	1.26	5.13	2.492*	1.01	6.13
IBS subgroups						
IBS-U (ref)						
IBS-C	0.519	0.16	1.67	0.534	0.14	2.00
IBS-D	0.671	0.24	1.92	0.542	0.17	1.71
IBS-M	0.955	0.26	3.58	0.607	0.32	2.79

IBS-SSS: Irritable bowel syndrome severity scoring system; PHQ-15: Patient Health Questionnaire-15;

IBS-D: IBS with diarrhea; IBS-C: IBS with constipation; IBS-M: mixed IBS; IBS-U: unsubtyped IBS.

^aMen = 1, Women = 2.

^bDichotomous variable No = 0, Yes = 1.

Significant at level * $P < .05$, ** $P < .01$, *** $P < .001$.

with IBS as compared to controls without functional GI disorders. When the authors controlled for demographic factors and mood disorders, the OR for having IBS while at the same time having atopic disease decreased to 1.4 from 1.66, but the model remained statistically significant.⁶ Additional studies have demonstrated a 20% increased prevalence of IBS among patients with asthma²⁸ and that the prevalence of IBS was 30% in asthmatic patients compared to 13% in a control group.²⁹ Meanwhile, some studies report even higher prevalence of atopic symptoms in patients with IBS: a study by Tobin et al. reported seasonal allergic rhinitis in 80% of IBS patients as compared to 22% in our study.¹⁸ Thus, atopy and atopy-related symptoms are frequent in IBS, but the reported prevalence varies between studies, which may be explained by different definitions of atopy and by studying dissimilar populations (eg, not primarily defined as patients with IBS but rather as having gastrointestinal complaints, or by using different versions of the ROME criteria for the diagnosis of IBS).

In the univariate analyses, we did not find any difference in IBS symptoms between atopic and non-atopic IBS patients. The regression analysis further supported our findings that atopy is not linked to IBS symptom severity. In the simple linear regression analysis, being woman, having severe somatic symptoms and reporting a high number of food items causing GI symptoms were significantly associated with IBS symptom severity, which is in line with previous research.^{10,30-32} Neither in the simple nor the multivariable adjusted analyses did we find any significant association between IBS-SSS and atopy, indicating little or no causal effect of atopy itself on IBS symptom severity. Our findings are in contrast to a previous study demonstrating increased IBS symptom severity among IBS patients with "allergic factors".¹⁷ The study by Vivinus-Nebot et al. which reported positive associations between allergic factors and IBS based their findings on a different definition, ie, they defined a background of allergy when patients fulfilled at least 3 of the following criteria: self-reporting of food allergy, personal and familial history of atopic

TABLE 5 Simple linear regression analysis on the association of self-reported atopy and other potential predictors with IBS symptom severity among patients with IBS

	Bivariate analysis		
	IBS-SSS B (95% CI)	Adjusted R ²	P value
Self-reported atopy ^a	4.96 (−18.52, 28.45)	0.001	.677
Gender ^b	−51.77 (−77.70, −25.84)	0.062	<.001
Age	0.53 (−0.45, 1.50)	0.001	.291
PHQ-15	9.45 (7.30, 11.59)	0.255	<.001
Total IgE	−0.07 (−0.20, 0.06)	0.000	.303
Total eosinophil count	−5.45 (−90.24, 79.35)	−0.005	.899
Self-reported food allergy/intolerance ^a	2.70 (−18.81, 24.21)	−0.004	.805
Number of food items causing GI symptoms	3.19 (1.77, 4.60)	0.079	<.001

IBS-SSS, Irritable bowel syndrome severity scoring system; PHQ-15, Patient Health Questionnaire-15; IgE, Immunoglobulin E; GI, gastrointestinal.

^aDichotomous variable Yes/No.

^bWomen = 1, Men = 2.

disease, elevated total or specific IgE against food or airborne antigens, blood eosinophilia, or positive skin prick tests. We chose to use the personal history of atopy as our main variable, assessing the other variables as covariates. Although atopic manifestations might occur during any point in life, it is more common that it develops during early childhood.³³ During early and middle adulthood, respiratory and skin manifestations are more closely related to occupational exposures, lifestyle, and tobacco smoking,³³ thus making the personal history of atopic manifestations more reliable than using the present status of atopic disease.

Having self-perceived food allergy/intolerance, when assessed as “yes” or “no”, was reported in 19% of all IBS patients, which is far less than those reporting GI symptoms to certain foods, 87% of all IBS patients. The discrepancy in reporting might be due to how one defines food-related reactions; a pronounced food allergy reaction or an enzymatic deficiency, such as having lactose intolerance, might be more associated with the term “food allergy/intolerance” compared to the more non-specific responses in individuals with IBS after intake of food. More atopic patients than non-atopic patients did report self-perceived food allergy/intolerance, although, there were no differences in the number of food items reported to cause GI symptoms between these groups. This highlights the importance of assessing if and which foods affect GI symptoms specifically, rather than only assessing the presence of food intolerances, when studying the severity of IBS symptoms.

TABLE 6 Multiple linear regression analyses on the association of self-reported atopy with IBS symptom severity, adjusted for covariates, among patients with IBS

	Multivariable analysis 1 ^b	Multivariable analysis 2 ^c	Multivariable analysis 3 ^d
	IBS-SSS B (95% CI)	IBS-SSS B (95% CI)	IBS-SSS B (95% CI)
Self-reported atopy ^a (full model)	−0.86 (−24.04, 22.32) ^e	−11.53 (−32.20, 9.14) ^f	−8.56 (−30.19, 13.73) ^g
Gender	−52.75 (−79.07, −26.43) ^{***}	−32.76 (−52.63, −4.00) [*]	−18.50 (−43.70, 6.67)
Age	0.61 (−0.34, 1.57)	0.48 (−0.37, 1.32)	0.43 (−0.45, 1.30)
PHQ-15		8.86 (6.63, 11.10) ^{***}	8.40 (6.14, 10.65) ^{***}
Total IgE			−0.02 (−0.13, 0.10)
Total eosinophil count			−27.20 (−99.89, 45.48)
Self-reported food intolerance ^a			3.07 (−16.33, 22.45)
Number of food items causing GI symptoms			2.33 (1.02, 3.63) ^{***}

IBS-SSS: Irritable bowel syndrome severity scoring system; PHQ-15: Patient Health Questionnaire-15; IgE: Immunoglobulin E; GI: gastrointestinal.

^aDichotomous variable Yes/No.

^bAdjusted R² = 0.061.

^cAdjusted R² = 0.269.

^dAdjusted R² = 0.299.

^eModel adjusted for gender and age.

^fAdjusted for gender, age and PHQ-15.

^gAdjusted for gender, age, PHQ-15, total IgE, total eosinophil count, self-reported food intolerance and number of food items causing GI symptoms.

Significant at level *P < .05, **P < .01, ***P < .001.

As we did not find clear evidence for a link between IgE-mediated allergy and food intolerance, other non-IgE-mediated hypersensitivity responses may be accountable for symptom generation in this patient group. The role of IgG- and IgG4-mediated hypersensitivity has been studied in IBS patients,^{34,35} and it has been suggested that a combination of specific IgG4 and IgE antibodies to food allergens may be useful in evaluating patients with adverse reactions to food.³⁶ Another possible explanation of the discrepancy between having self-perceived food intolerance and food allergy could be the findings of an intestinal IgE-mediated response in patients with food-related gastrointestinal symptoms, without increased levels of IgE in peripheral blood.^{37,38} Also, the role of fermentable carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides and polyols: FODMAPs) for IBS symptom generation has been frequently discussed recently.³⁹⁻⁴¹ These represent carbohydrates that are not fully absorbed in the small intestine, but will rather act as substrates to the gut microbiota in the colon, causing excessive gas production and water retention. This will lead to a distention of the colon and, in IBS patients with visceral hypersensitivity, potentially lead to symptom generation.⁴²

The major strength of this study compared to many other studies is that we had access to a wide range of both objective and subjective measures, including serum levels of IgE in a large sample. Besides having access to data regarding GI symptoms, we also measured several aspects of bodily illness and psychological symptoms, being able to characterize our study participants in multiple dimensions. A limitation of this study is the relatively small number of subjects in our control group, and we might therefore not have had sufficient power to detect true differences in the prevalence of atopy between patients with IBS compared to our control group. As the control group was composed of individuals who volunteered to participate in a rather rigorous clinical study, we cannot rule out that this was a selected group of people that might be more health conscious than the general population. We acknowledge that the reporting of atopic disease might therefore have been more prevalent in this group, so the question if atopic disease is more common in individuals with IBS than in the general population still remains unanswered. Moreover, as we recruited patients with IBS from our specialized unit for functional GI disorders, the generalizability of our study population might also be questioned. However, the wide range in age and symptom pattern, suggests that we recruited a representative IBS cohort. However, the main objective of this study was to evaluate the importance of presence of atopy within the IBS population, and relation with various clinical factors. A final limitation is that we were not able to measure the impact of mucosal mast cells, which might have led us to further understanding of the role of mast cells in symptom generation.

In conclusion, atopic disease is common in patients with IBS, but not associated with the severity of IBS symptoms. Compared to non-atopic IBS patients, atopic IBS patients had an increased prevalence of self-reported food allergy/intolerance and more severe somatic symptoms. Our study does not support a strong involvement of

IgE-mediated food reactions in the pathophysiology of IBS. However, the role of non-IgE-mediated food hypersensitivity in patients with IBS needs to be further investigated.

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AUTHOR CONTRIBUTION

MS guarantor of article; MS, HT, LÖ, and SS designed the study; KW, LB, and MM collected the data; UB contributed with allergy-specific questionnaires and; SN performed the statistical analysis of the data and wrote the paper; AW critically revised the paper. All authors interpreted the results and critically reviewed the manuscript.

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