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Post-infectious and sporadic functional gastrointestinal disorders have different prevalences and rates of overlap: results from a controlled cohort study three years after acute giardiasis

Running title: Functional GI disorders following giardiasis

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Key Messages

- Functional gastrointestinal disorders (FGID) are classified based on reported symptoms, and there is an ongoing process to improve the phenotyping of these conditions. We have investigated the characteristics and overlap of FGID in a large cohort of patients and controls three years after acute giardiasis.
- FGID following acute giardiasis have different characteristics and more overlap than sporadic FGID in the control group,
- These results represent a significant addition to our knowledge about the epidemiology and reported symptoms of FGID.

ABSTRACT

BACKGROUND:

Irritable bowel syndrome (IBS) is a common complication following gastroenteritis, and a high prevalence of post-giardiasis IBS has previously been reported. This study aims to investigate the prevalence, adjusted relative risk (RRadj) and overlap of different functional gastrointestinal disorders (FGID) according to Rome III criteria following infection with *Giardia lamblia*.

METHODS:

All patients ≥ 18 years of age with verified giardiasis during an outbreak in 2004, and a control group matched by age and gender, were mailed a questionnaire three years later.

KEY RESULTS:

The prevalence of functional dyspepsia (FD) was 25.9% in the exposed and 6.9% in the control group, RRadj: 3.9 (95% CI: 3.1–4.8). The prevalence of IBS was 47.9% and 14.3% respectively, RRadj: 3.4 (95% CI: 3.0–3.8). Prevalence of other gastrointestinal symptoms ranged from 70.0% vs. 39.7% for bloating (RRadj: 1.8) to 8.3% vs. 2.9% for nausea (RRadj: 3.0) in the G*iardia* and the control group, respectively. Among individuals fulfilling criteria for IBS 44% in the exposed group and 29% in the control group also fulfilled criteria for FD. IBS subtypes based on Rome III criteria (stool consistency) showed poor agreement with subtypes based on frequency of bowel movements (Kappa-values: 0.17 and 0.27).

CONCLUSIONS & INFERENCES:

There were high prevalences and RRs of IBS, FD and other gastrointestinal symptoms following acute giardiasis, and a high degree of overlap between the disorders. The agreement

between different IBS subtype criteria varied, and there were also differences between the exposed and control group.

Key words: functional dyspepsia, *Giardia lamblia*, irritable bowel syndrome, post-infectious sequela, Rome III criteria.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are widespread in the population and in clinical practice (1, 2). The most common and widely investigated disorder is irritable bowel syndrome (IBS) (3), but functional dyspepsia (FD) and other conditions are also common (4, 5). The classification of these disorders has been revised on several occasions, reflecting the challenges in optimizing its usefulness for research and clinical practice (6). The current Rome III-criteria have also been criticized for poor validity, insufficient ability to discriminate FGID from organic disease, and limited agreement of the populations identified compared with previous criteria, and the process to reach a better set of criteria continues (7-9).

The Rome III criteria define 28 different FGIDs in adults (10), and it has proven difficult to identify features and mechanisms that are unique to each diagnosis. There is considerable overlap in the prevalence of IBS and FD, and it has been suggested that the two conditions share some pathophysiological pathways (11, 12). Furthermore, longitudinal studies have demonstrated that patients with chronic gastrointestinal symptoms that meet criteria for a specific FGID at one time may later receive a different diagnosis due to fluctuations in symptoms (13, 14).

IBS is often preceded by and considered a complication of infectious gastroenteritis (15). Increased risk of other FGIDs, like FD, has also been demonstrated after outbreaks of gastroenteritis (16). Given the important role of infections in the development of FGID, outbreaks provide good opportunities to increase our knowledge about these conditions.

In the city of Bergen, Norway, there was a large outbreak of gastroenteritis caused by the parasite *Giardia lamblia* in 2004 (17). *Giardia* is widespread around the globe, and in several regions giardiasis is endemic, especially in areas where hygiene and water sanitation is poor. In Europe and North America *Giardia* is a commonly identified pathogen in waterborne

outbreaks of disease (18). During the outbreak in Bergen, 2 500 patients were treated for giardiasis, and 1 252 had a laboratory confirmed diagnosis (19). This was the first outbreak of such magnitude in Norway, and the well-defined exposure gives a unique opportunity to study the epidemiology of FGIDs following infection with an identified pathogen. We have previously reported a strong association between acute giardiasis and both IBS and chronic fatigue three years after the outbreak (19).

The aim of this study was to investigate and report the prevalence, overlap and associations of FD, IBS and other GI symptoms in patients three years after acute giardiasis compared to that of a control group, and to explore the agreement of subtyping IBS based on stool consistency (as in Rome III criteria) and based on frequency of bowel movements.

METHODS

Participants

The data were collected in 2007 from a cohort of 1252 patients with acute giardiasis in 2004 and 3594 controls, matched by age and gender, and who were not ill during the outbreak. We have previously reported the prevalence of chronic fatigue and IBS in the whole cohort (19). The present study was restricted to adults above the age of 18, including 1184 participants with previous giardiasis and 3380 controls. All participants were mailed a questionnaire three years after the outbreak. Non-respondents were mailed again one month later.

Variables

The main outcome variables are FD and IBS with subgroups according to Rome III criteria (10). The questions from the Rome III Diagnostic Questionnaire (20) were translated into Norwegian according to a standardized procedure (19). We also recorded the outcomes

nausea, bloating, diarrhea, constipation and foul smelling stools/flatulence. We included the demographic variables gender, age (categorized into 20-years groups), marital status (four categories), educational level (three categories), employment status (eight categories, reduced to four in the analyses) and whether the person had been a student during the outbreak.

Functional dyspepsia

The Rome III diagnosis of FD is based on presence of symptoms related to the upper abdomen (postprandial fullness, early satiation and epigastric pain or burning) and exclusion of pathology that may explain the symptoms (21). The design of this study did not include investigation of patients, but in order to reduce misclassification we asked the participants to name any esophageal or gastric disorder diagnosed by a physician within the previous three years. A list of disorders defined to explain the symptoms, together with a description of the process to reach the decision, is provided as supplementary material.

Irritable bowel syndrome

A diagnosis of IBS is made when there is recurrent abdominal pain or discomfort at least three days per month in the last three months, and associated with at least two of three criteria related to defecation (onset associated with a change in frequency or consistency of stool, or improvement with defecation) (22). The Rome III criteria divide IBS into four subgroups based on stool consistency: "IBS with diarrhea" (loose or watery stools at ≥ 25% of bowel movements, and hard or lumpy stools at < 25 % of bowel movements) (IBS-D), "IBS with constipation" (hard or lumpy stools at ≥ 25 % of bowel movements, and loose or watery stools at < 25% of bowel movements) (IBS-C), "mixed IBS" (both loose/watery stools and hard/lumpy stools each at ≥ 25% of bowel movements) (IBS-M), and unsubtyped IBS (without abnormality of stool consistency to meet criteria for the others) (IBS-U). The

previous Rome II criteria also included criteria on straining/urgency during bowel movements and frequency of bowel movements for subtyping IBS (23). We didn't have information on straining/urgency, but for further exploration of the characteristic of IBS in the two groups we also subdivided IBS according to frequency of bowel movements. "Frequent bowel movements" is defined as four or more bowel movements a day at least "sometimes", and "infrequent bowel movements" as fewer than three bowel movements a week at least "sometimes". Finally we subtyped IBS approximated to Rome II criteria (without data on straining/urgency). Diarrhea predominant IBS (d-IBS) is defined as: i) either frequent bowel movements and loose stools, or both, in the absence of both infrequent bowel movements and hard stools, or ii) both frequent bowel movements and loose stools in the presence of infrequent bowel movements. Constipation predominant IBS (c-IBS) is defined as: i) either infrequent bowel movements or hard stools, or both, in the absence of both frequent bowel movements and loose stools, or ii) both infrequent bowel movements and hard stools in the presence of either infrequent bowel movements and loose stools. Patients not fulfilling the criteria for d-IBS or c-IBS were categorized as having alternating or mixed IBS (a-IBS).

Other functional gastrointestinal symptoms

For the variables "bloating", "nausea", "diarrhea" and "constipation" we used questions from the Rome III Questionnaire. We did not ask about duration of these symptoms and therefore the variables are not identical to disorders defined by the Rome III criteria, as they require that the symptoms have been present for the last six months. Not entering these questions was a deliberate choice to limit the size of the questionnaire and make it feasible for this kind of study. "Bloating" is defined as having this symptom at least 2-3 days a month, and this is the same frequency that is used for "functional bloating" (22). Bloating more often than one day a week we describe as "severe bloating". "Nausea" is defined as reporting nausea more than

once a week, the same as in "chronic idiopathic nausea" (21). "Diarrhea" is defined as loose or watery stools ≥ 75% of bowel movements and four or more bowel movements at least "sometimes". The Rome III criteria for "functional diarrhea" require that IBS is not present, but since we wanted to look at overlap we didn't apply this criterion. "Constipation" is defined as fewer than three defecations a week at least "often".

We included "foul-smelling stools or flatulence" as a variable because this is a symptom that several patients complained about during the outbreak, and asked how often, within the last three months, foul smell from stool or flatus affected activities of daily living (for instance avoiding social contact). In the manner of the Rome III Questionnaire there was an option of seven graded responses, and a response of "one day a week" or more often was defined as a positive response.

Analyses and statistical methods

Non-respondents were excluded for all analyses, as were pregnant participants. Participants with missing data were excluded from the analyses involving that particular variable.

Association in 2×k tables was tested by Pearson's chi²-test. Results are reported as relative risks (RR) with 95% confidence intervals (CI). Continuous variable means were compared using Gosset's t test (24). The outcome variables were analyzed separately with respect to the risk factors and possible interactions using multiple logistic regression producing adjusted odds ratios (OR) with 95% CI (25), which were converted to RRs and corresponding CIs by the method of Zhang and Yu (26). Effect modification was tested by the Breslow-Day test for homogeneity of ORs after stratification. Confounding was evaluated by use of the Mantel-Haenszel common OR and multiple logistic regression analyses, and variables found to be confounders were then controlled for by multiple logistic regression.

Agreement between IBS subtypes was tested using the Kappa statistic (κ), with 95% CI. A κ-value of 1 implies perfect agreement, values > 0.8 indicate very good agreement, 0.61-0.8 good agreement, 0.41-0.6 moderate agreement, 0.21-0.4 fair agreement, and < 0.21 very poor agreement (27). When analyzing agreement between Rome III and Rome II criteria we combined IBS-M and IBS-U, and compared the prevalence to that of a-IBS.

Concordance rates, the proportions of patients belonging to the same or comparable subtypes by different classifications (IBS-D and IBS with frequent bowel movements, IBS-C and IBS with infrequent bowel movements, and Rome III with Rome II subtype) were calculated.

Level of statistical significance was set at 0.05, and all tests were two-sided. All analyses were done using IBM SPSS Statistics version 23.

Ethical aspects

This study has been approved by the Regional Committee for Medical and Health Research Ethics (project 150.07), and by the Ombudsman for Privacy in Research, Norwegian Social Science Data Services (project 17014).

RESULTS

The response rates were 66% (781/1184) among exposed patients and 33% (1099/3380) among controls. Respondents were older than non-respondents (37.1 vs. 34.6 years, $p < 0.001$) and the proportion of females was higher (66.4% vs. 57.4%, $p < 0.001$). Four controls were excluded because they reported having had giardiasis verified by a physician during the outbreak, and 64 female participants were excluded because they were pregnant, leaving 749 exposed and 1063 controls for analyses. Characteristics of included participants are shown in table 1.

Irritable bowel syndrome and functional dyspepsia

The prevalence of IBS in the whole cohort has been reported previously (19). The prevalence of IBS among the adults included in this study was 47.9% (339/707) in the exposed and 14.3% (149/1042) in the control group, with an adjusted RR of 3.4 (95% CI: 3.0–3.8). The prevalence of FD was 25.9% (189/730) in the exposed and 6.9% (72/1049) in the control group, corresponding to an adjusted RR of 3.9 (95% CI: 3.1–4.8) for having FD three years after the outbreak for the exposed compared to the controls (table 2). The majority with FD also fulfilled the criteria for IBS. The prevalence of FD without concomitant IBS was 3.8% in the *Giardia* group and 2.5% in the control group, and the proportion of patients with FD that also had IBS was 85% and 62%, respectively in the two groups (tables 3 and 4).

Other functional gastrointestinal disorders and symptoms

Prevalences of other gastrointestinal symptoms are also shown in table 2. The prevalences of bloating, diarrhea, nausea and foul smelling stools were significantly higher in the exposed group, whereas the prevalence of constipation was similar in the two groups. The proportion of participants with these disorders that also had IBS ranged from 63% (bloating) to 88% (nausea) in the *Giardia* group, and from 28% (constipation) to 62% (functional dyspepsia) in the control group. The total overlap between the different FGID and symptoms in patients with complete datasets (and excluding pregnant participants) are shown for the *Giardia*-exposed in table 3 and the controls in table 4.

Subtyping IBS

Both among the exposed and the controls IBS-D and IBS-M were most prevalent, but there were differences between the two groups. The proportion with IBS-D and IBS-M was higher and the proportion with IBS-C was lower among the exposed than among the controls (table

5). This subtyping is based on stool consistency, and the observed differences between the groups were results of a larger proportion of individuals with IBS having loose stools in the exposed group compared to the controls. The proportion with hard stools was similar in the two groups (table 5), and the higher proportion of IBS-C among controls was due to less participants also having loose stools and thereby fulfilling criteria for IBS-M.

In the analysis of IBS subtyped by stool frequency, based on the presence of "frequent" or "infrequent" bowel movements, there was a significantly higher proportion of "IBS with frequent bowel movements" in the *Giardia*-group, and of "IBS with infrequent bowel movements" in the control group (table 5). This corresponded with the finding that among *Giardia* exposed with IBS the prevalence of "frequent bowel movements at least sometimes" was significantly higher compared to controls with IBS (69.9% vs. 47.7%, $p < 0.001$), and that the prevalence of "infrequent bowel movements at least sometimes" was significantly lower among *Giardia* exposed compared to controls with IBS (13.9% vs. 24.2%, $p = 0.005$).

The agreement between subtyping IBS based on stool consistency according to Rome III criteria and the alternative subtyping based on frequency of bowel movements was very poor among the exposed ($\kappa = 0.17$) (table 6) and fair among the controls ($\kappa = 0.27$) (table 7), but the 95% CI for the κ-values overlap (0.11–0.23 vs. 0.18–0.36). In the subtyping according to Rome III criteria 46% of the *Giardia*-exposed IBS-patients reported both hard and loose stools fulfilling criteria for IBS-M, whereas in the alternative subtyping only 7% reported both frequent and infrequent bowel movements. Only 6% were classified with IBS-U according to Rome III criteria, but in the alternative subtyping 24% reported no abnormality in frequency of bowel movements sufficient to subtype them.

The agreement between subtyping based on Rome III and Rome II criteria was different in the two groups. It was very good in the *Giardia* group (κ = 0.86, 95% CI: 0.81–0.91) (table 8), and good in the control group (κ = 0.71, 95% CI: 0.61–0.80) (table 9).

Gender differences

There were significant gender differences in the prevalence of IBS, but gender was not an effect modifier. We have already reported this in the whole cohort (19), and in this study in adults the prevalence wa 51.4% in females and 41.7% in males in the exposed group (p = 0.013), and 16.3% and 10.6%, respectively, in the control group (p = 0.012). For FD there were no gender differences in the prevalence neither in the exposed group (27.7% in females vs. 22.5% in males, p = 0.131) nor in the control group (7.3% vs. 6.0%, p = 0.414).

DISCUSSION

There were three main results in this paper: First, we found a high prevalence and RR of FD three years after acute giardiasis, as well as IBS which we have shown earlier (19), and other gastrointestinal symptoms. Post-giardiasis IBS was characterized by more loose stools and frequent bowel movements than sporadic IBS. Second, there was a high degree of overlap between IBS and other FGID, and this was more prominent in the *Giardia* group than among controls. Third, the agreement between IBS subtypes based on stool consistency according to Rome III criteria and frequency of bowel movements was only fair or very poor. When combining these characteristics according to Rome II criteria the agreement was better, and more so in the group with previous *Giardia* infection than in the control group.

Strengths and weaknesses

The outbreak of giardiasis in Bergen was well defined with a large population exposed to a verified pathogen for a restricted time period. It was one of the largest *Giardia* outbreaks described in the scientific literature, and the high number of infected individuals offers the opportunity to study the consequences in greater depth. An outbreak like this was not anticipated and the research protocol had to be set up at a time where the major focus was on managing the outbreak. The three year time gap after the acute infection made any data on previous FGID unreliable because of potential recall bias. Also, defining incident cases is difficult since IBS and other FGID are prevalent and post-giardiasis cases might manifest with aggravated or new symptoms. We did not attempt to give the incidence of post-giardiasis FGID, instead we included a control group and compared prevalences in the two groups.

The response rates are comparable to those observed in similar studies (28, 29), but the response rate of 33% in the control group is still low and introduces a risk of bias. However, the prevalence of IBS in this group was similar to what has been found earlier in the general Norwegian population (30). The exposure to acute giardiasis during the outbreak may have led to increased awareness and a tendency towards reporting more gastrointestinal symptoms in the period to follow, but we did not find it plausible that this should explain a substantial proportion of the high prevalence of post-giardiasis complications, something that had not been described earlier and therefore was not anticipated (19). A key objective of this study was to explore the pattern of symptoms in affected individuals, and this should be less influenced by this kind of bias.

Ideally, persistent infection should be ruled out as chronic giardiasis may give FGID-like symptoms (31). The design of the study did not make this possible, but other studies have not found evidence for chronic infection in this population (32-34).

Interpretation

There was a higher prevalence of all outcomes except constipation in the exposed group compared to controls. This shows that the long term symptoms after giardiasis are not restricted to IBS, which is in line with the findings after outbreaks of gastroenteritis caused by Salmonella (28) and campylobacter/Enterohemorrhagic E. coli (EHEC) (35), and in a systematic review that documents increased risk of FD after acute gastroenteritis (16).

There was substantial overlap between the different FGIDs in both groups, but the overlap between IBS and other FGIDs was more prominent in the exposed group suggesting that IBS-criteria more precisely cover a common post-infectious condition, and that the abdominal symptoms and possible mechanisms behind them are more diverse in sporadic IBS.

In addition to IBS and FD, where the main symptom by definition is pain or discomfort, the most prevalent manifestations of post-giardiasis FGID were looser stools and more frequent bowel movements. These features, especially stool consistency, but also frequency of bowel movements, have been shown to be associated with colonic transit time (36). The prevalence of patients reporting loose stools was high in the exposed group and significantly more patients had IBS-D and IBS-M compared to the controls. The higher proportion of IBS-C among controls was actually not explained by higher prevalence of hard stools, but by a lower prevalence of loose stools and less IBS-M.

The challenges related to subtyping IBS was addressed in the revision leading up to the current Rome III criteria (22, 37). One result of the revision was that the criteria were simplified, and the items related to frequency of bowel movements and straining/urgency were abandoned. Several groups have compared the subtype distribution of IBS based on Rome II and Rome III criteria (38-41), but none of these have reported the actual prevalence of different frequencies of bowel movements. In the current study we found good agreement between subtypes classified by Rome II and Rome III criteria, but the agreement was fair or poor when comparing stool consistency and frequency of bowel movements. These findings could have implications for the understanding of IBS and for possible treatments, something that is supported by the fact that the U.S. Food and Drug Administration calls for change in stool consistency for clinical evaluation of drugs for treatment in IBS-D, but recommends frequency of bowel movements in IBS-C (42).

IBS is a chronic condition and classification has relied on patient retrospectively reporting prevalence of bowel movements and stool form. It has been shown that this correlates poorly with the findings when using a stool diary (38-41), but a couple of issues are still unclear. We know that agreement is poor for stool consistency, since the studies report Rome III subtypes that are based on this characteristic, but we don't know how the agreement is for frequency of bowel movements. Further, the use of a stool diary covers a short period of time, typically 14 days, while retrospective questionnaires focus on the last three months. If the questionnaires covered the same short period they are likely to produce results with better agreement. It could also be that a retrospective account of symptoms over a period of three months gives a more precise description of the chronic condition. The repeated use of stool diaries in the same patients have demonstrated that IBS subtypes change in more than 50% of patients within one year (38).

The results presented in this study differ markedly from other studies comparing classifications of IBS subtypes, and this emphasizes that caution should be made when interpreting data on symptoms patterns in IBS. We recruited patients that had suffered acute giardiasis three years earlier and not because they had gastrointestinal symptoms. Our focus was on post-infectious IBS, and cases were defined based on Rome III criteria. Other studies have included patients seen in gastroenterological clinics and as a result there could be a selection of symptom patterns in these populations with sporadic IBS, and also these studies defined IBS by Rome II criteria (38-41).

Generalizability

We have shown a high risk of different FGIDs and gastrointestinal symptoms after acute giardiasis. This study was performed in a population with verified giardiasis in an area where *Giardia* is rare; hence, we have made the assumption that most participants were previously unexposed. The burden of disease caused by giardiasis is much larger where the parasite is endemic, but there the population is exposed at a younger age and the clinical course and possible complications may differ. Further research on giardiasis in endemic areas is needed to get a better understanding of the impact of the disease there. Increased risk of IBS has also been shown after bacterial (28, 29, 43) and viral (44) gastroenteritis, and our findings add to the knowledge of post-infectious FGIDs in general. The differences between the exposed and the control group suggest that post-infectious FGIDs differ from sporadic FGIDs, and this should have implications for future research on epidemiology, mechanisms and possibly treatment.

The pronounced overlap between different FGIDs, the differences between FGIDs in the two groups, and the challenges shown when subtyping IBS, are all aspects that should be acknowledged in the process towards a better classification of these disorders.

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DISCLOSURE

The authors have no competing interests.

AUTHOR CONTRIBUTION

KAW contributed to the study concept and design of the study, acquisition, analysis and interpretation of data, and drafted the manuscript. KH, NL and KM contributed to the study concept and design, acquisition of data, and to critical revision of the manuscript for important intellectual content. GEE contributed to the analysis and interpretation of data. TH contributed to the study concept and design, and to critical revision of the manuscript for important intellectual content. GR contributed to the study concept and design, acquisition of data, to critical revision of the manuscript for important intellectual content, obtaining funding, and study supervision.

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Table 1. Characteristics of a group of individuals exposed to *Giardia* infection during an outbreak three years earlier and a control group that did not contract the infection.

Characteristics	**Exposed (*N* = 749)**	**Controls (*N* = 1063)**	***p* value**
Gender, *n* (%)			
Male	259 (34.6)	372 (35.0)	0.855*
Female	490 (65.5)	691 (65.0)	
Age			
Mean, (range)	37.4 (19-94)	37.2 (19-89)	0.732†
Age 19–39, *n* (%)	497 (66.4)	707 (66.5)	
Age 40–59, *n* (%)	187 (25.0)	276 (26.0)	0.221*
Age 60–79, *n* (%)	56 (7.5)	76 (7.3)	
Age 80–99, *n* (%)	9 (1.2)	4 (0.4)	
Marital status, *n* (%)			
Single	240 (32.2)	263 (24.8)	
Married	464 (62.2)	747 (70.3)	0.004*
Divorced	33 (4.4)	41 (3.9)	
Widowed	9 (1.2)	11 (1.0)	
Education, highest level, *n* (%)			
Primary school	23 (3.1)	44 (4.2)	
Secondary school	153 (20.8)	293 (27.8)	0.001*
University	559 (76.1)	717 (68.0)	
Employment status, *n* (%)			
Worker	548 (73.4)	849 (80.2)	
Student, *n* (%)	110 (14.7)	99 (9.4)	< 0.001*
Unemployed/retired	68 (9.1)	95 (9.0)	
Other	21 (2.7)	15 (1.4)	
Student during the outbreak, *n* (%)			
Yes	271 (36.7)	255 (24.3)	< 0.001*
No	468 (63.3)	794 (75.7)	

Exposed and controls were matched by gender and age.
*Pearson chi²-test from 2×k table.
†Gosset's t-test for independent samples

Table 2 Functional gastrointestinal disorders in a group of 749 adult patients who had acute giardiasis during an outbreak three years earlier, and a control-group of 1063 who did not contract the infection

	All*	*Giardia*-group		Control-group		Unadjusted		Adjusted†	
Condition	**N**	***n***	**(%)**	***n***	**(%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
IBS	1749	339	(47.9)	149	(14.3)	3.4	(2.8–4.0)	3.4	(3.0–3.8)
Functional dyspepsia	1779	189	(25.9)	72	(6.9)	3.8	(2.9–4.9)	3.9	(3.1–4.8)
Bloating	1762	498	(70.0)	417	(39.7)	1.8	(1.6–1.9)	1.8	(1.7–1.9)
Severe bloating	1762	272	(38.3)	126	(12.0)	3.2	(2.6–3.9)	3.2	(2.7–3.7)
Diarrhea	1760	100	(14.0)	35	(3.3)	4.2	(2.9–6.1)	4.4	(3.0–6.1)
Constipation	1761	22	(3.1)	47	(4.5)	0.7	(0.4–1.1)	0.7	(0.4–1.2)
Nausea	1763	59	(8.3)	30	(2.9)	2.9	(1.9–4.4)	3.0	(2.0–4.7)
Foul smell	1759	103	(14.5)	38	(3.6)	4.0	(2.8–5.7)	4.1	(2.9–5.7)

*Number available for analyses differs for different diagnoses due to missing data.
†Adjusted for gender, age, marital status, educational level, employment status and being a student during the outbreak, in logistic regression.
Abbreviations: RR: Relative risk. CI: Confidence interval. IBS: Irritable bowel syndrome.

Table 3 Overlap between different functional gastrointestinal disorders and symptoms in 688 patients three years after acute giardiasis, *n* (%)

	Total	**IBS**	**FD**	**Bloating**	**Diarrhea**	**Constipation**	**Nausea**	**Foul smell**
IBS	331 (100)	-	144 (44)	305 (92)	71 (21)	15 (5)	49 (15)	77 (23)
FD	170 (100)	144 (85)	-	160 (94)	54 (29)	9 (5)	37 (22)	62 (36)
Bloating	481 (100)	305 (63)	160 (33)	-	83 (17)	21 (4)	51 (11)	96 (20)
Diarrhea	95 (100)	71 (75)	49 (52)	83 (87)	-	2 (2)	16 (17)	39 (41)
Constipation	22 (100)	15 (68)	9 (41)	21 (95)	2 (9)	-	5 (23)	4 (18)
Nausea	56 (100)	49 (88)	37 (66)	51 (91)	16 (29)	5 (9)	-	27 (48)
Foul smell	99 (100)	77 (78)	62 (63)	96 (97)	39 (39)	4 (4)	27 (27)	-

Abbreviations: IBS: Irritable bowel syndrome. FD: Functional dyspepsia.

Table 4 Overlap between different functional gastrointestinal disorders and symptoms in 1026 controls without previous giardiasis, *n* (%)

	Total	**IBS**	**FD**	**Bloating**	**Diarrhea**	**Constipation**	**Nausea**	**Foul smell**
IBS	146 (100)	-	43 (29)	117 (80)	17 (12)	13 (9)	14 (10)	15 (10)
FD	69 (100)	43 (62)	-	6 (81)	13 (19)	8 (12)	11 (16)	11 (16)
Bloating	403 (100)	117 (29)	56 (14)	-	27 (7)	33 (8)	26 (6)	30 (7)
Diarrhea	33 (100)	17 (52)	13 (39)	27 (82)	-	1 (3)	4 (12)	8 (24)
Constipation	46 (100)	13 (28)	8 (17)	33 (72)	1 (2)	-	2 (4)	1 (2)
Nausea	30 (100)	14 (47)	11 (37)	26 (87)	4 (13)	2 (7)	-	6 (20)
Foul smell	36 (100)	15 (42)	11 (31)	30 (83)	8 (22)	1 (3)	6 (17)	-

Abbreviations: IBS: Irritable bowel syndrome. FD: Functional dyspepsia.

Table 5 Irritable bowel syndrome (IBS) subtyping according to Rome III criteria (based on stool consistency) and based on frequency of bowel movements (at least sometimes) among 488 study participants with IBS in Bergen, Norway 2007

	***Giardia*-group N = 339**		**Control-group N = 149**		
Criteria	***n***	***(%)***	**n**	**(%)**	***p* value***
Stool consistency					
Loose stools	287	(84.7)	104	(69.8)	< 0.001
Hard stools	188	(55.5)	81	(54.4)	0.823
Rome III subtype					
IBS-D	131	(38.6)	50	(33.6)	0.001
IBS-C	32	(9.4)	28	(18.8)	
IBS-M	156	(46.0)	53	(35.6)	
IBS-U	20	(5.9)	18	(12.1)	
Frequency of bowel movements					
Frequent at least sometimes	237	(69.9)	71	(47.7)	< 0.001
Infrequent at least sometimes	47	(13.9)	36	(24.2)	0.005
Alternative subtype					
IBS with frequent bowel movements	213	(62.8)	62	(41.6)	< 0.001
IBS with infrequent bowel movements	23	(6.8)	27	(18.1)	
IBS with both frequent and infrequent bowel movements	24	(7.1)	9	(6.0)	
IBS without abnormal frequency of bowel movements	79	(23.3)	51	(34.2)	

Abbreviations: IBS-D: IBS with diarrhea. IBS-C: IBS with constipation. IBS-M: Mixed IBS. IBS-U: Unsubtyped IBS.

*Pearson's chi²-test for 2×k table.

Table 6 Relationship between irritable bowel syndrome (IBS) subtyped by stool consistency according to Rome III criteria and IBS subtyped by frequency of bowel movements (at least "sometimes") among 339 patients who fulfilled Rome III criteria for IBS three years after acute giardiasis, *n* (%)

Rome III	IBS with frequent bowel movements	IBS with infrequent bowel movements	IBS with both frequent and infrequent bowel movements	IBS without abnormal frequency of bowel movements	Total
IBS-D	102 (78)	3 (2)	5 (4)	21 (16)	131 (100)
IBS-C	8 (25)	11 (34)	4 (13)	9 (28)	32 (100)
IBS-M	96 (62)	8 (5)	15 (10)	37 (24)	156 (100)
IBS-U	7 (35)	1 (5)	0 (0)	12 (60)	21 (100)
Total	213 (63)	23 (7)	24 (7)	79 (23)	339 (100)

Abbreviations: IBS-D: IBS with diarrhea. IBS-C: IBS with constipation. IBS-M: Mixed IBS. IBS-U: Unsubtyped IBS.

Concordance rate: 41.3%. $\kappa = 0.17$ (95% CI: 0.11–0.23).

Table 7 Relationship between irritable bowel syndrome (IBS) subtyped by stool consistency according to Rome III criteria and IBS subtyped by frequency of bowel movements (at least "sometimes") among 149 controls who fulfilled Rome III criteria for IBS, *n* (%)

Rome III	IBS with frequent bowel movements	IBS with infrequent bowel movements	IBS with both frequent and infrequent bowel movements	IBS without abnormal frequency of bowel movements	Total
IBS-D	35 (70)	1 (2)	1 (2)	13 (26)	50 (100)
IBS-C	9 (32)	11 (39)	0 (0)	8 (29)	28 (100)
IBS-M	14 (26)	13 (25)	8 (15)	18 (34)	53 (100)
IBS-U	4 (22)	2 (11)	0 (0)	12 (67)	180 (100)
Total	62 (42)	27 (18)	9 (6)	51 (34)	149 (100)

Abbreviations: IBS-D: IBS with diarrhea. IBS-C: IBS with constipation. IBS-M: Mixed IBS. IBS-U: Unsubtyped IBS.
Concordance rate: 44.3%. $\kappa = 0.27$ (95% CI: 0.18–0.36).

Table 8 Relationship between irritable bowel syndrome (IBS) subtyped by Rome III criteria and Rome II criteria among 339 patients who fulfilled Rome III criteria for IBS three years after acute giardiasis, *n* (%)

Rome III	**Rome II d-IBS**		**Rome II d-IBS**		**Rome II a-IBS**		**Total**	
IBS-C	128	(98)	0	(0)	3	(2)	131	(100)
IBS-C	0	(0)	24	(75)	8	(25)	32	(100)
IBS-M/U	7	(4)	9	(5)	160	(91)	176	(100)
Total	135	(40)	33	(10)	171	(50)	339	(100)

Abbreviations: IBS-D: IBS with diarrhea. IBS-C: IBS with constipation. IBS-M/U: Mixed IBS. d-IBS: Diarrhea predominant IBS. c-IBS: Constipation predominant IBS. a-IBS: Alternating IBS.

Concordance rate: 92.0%. $\kappa = 0.86$ (95% CI: 0.81–0.91).

Table 9 Relationship between irritable bowel syndrome (IBS) subtyped by Rome III criteria and Rome II criteria among 149 controls who fulfilled Rome III criteria for IBS, *n* (%)

Rome III	Rome II d-IBS		Rome II d-IBS		Rome II a-IBS		Total	
IBS-C	49	(98)	0	(0)	1	(2)	50	(100)
IBS-C	0	(0)	19	(68)	9	(32)	28	(100)
IBS-M/U	4	(6)	14	(20)	53	(75)	71	(100)
Total	53	(36)	33	(22)	63	(42)	149	(100)

Abbreviations: IBS-D: IBS with diarrhea. IBS-C: IBS with constipation. IBS-M/U: Mixed IBS. d-IBS: Diarrhea predominant IBS. c-IBS: Constipation predominant IBS. a-IBS: Alternating IBS.

Concordance rate: 81.2%. $\kappa = 0.71$ (95% CI: 0.61–0.80).