Observational Studies

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Prevalence of fibromyalgia 10 years after infection with *Giardia lamblia*: a controlled prospective cohort study

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Abstract

Objectives: To investigate whether acute infection with *Giardia lamblia* is associated with fibromyalgia 10 years after infection and whether fibromyalgia is associated with irritable bowel syndrome (IBS) and chronic fatigue (CF) in this setting.

Methods: A cohort study was established after an outbreak of *G. lamblia* in Bergen, Norway, 2004. Laboratory-confirmed cases and a matched control group were followed for 10 years. The main outcome was fibromyalgia 10 years after giardiasis, defined by the 2016 revisions of the fibromyalgia diagnostic criteria using the Fibromyalgia Survey Questionnaire (FSQ).

Results: The prevalence of fibromyalgia was 8.6% (49/572) among *Giardia* exposed compared to 3.1% (21/673) in controls ($p<0.001$). Unadjusted odds for having fibromyalgia was higher for *Giardia* exposed compared to controls (odds ratio (OR): 2.91, 95% confidence interval (CI): 1.72, 4.91), but adjusted for IBS and CF it was not (OR: 1.05, 95% CI: 0.57, 1.95). Among participants without CF the odds for fibromyalgia was 6.27 times higher for participants with IBS than those without (95% CI: 3.31, 11.91) regardless of exposure. Among participants without IBS the odds for fibromyalgia was 4.80 times higher for those with CF than those without (95% CI: 2.75, 8.37).

Conclusions: We found a higher prevalence of fibromyalgia among *Giardia* exposed compared to controls 10 years after the acute infection. Fibromyalgia was strongly associated with IBS and CF, and the difference between the exposed and controls can be attributed to the high prevalence of IBS and CF among the *Giardia* exposed. Notably, this study was not designed to establish causality between *Giardia* exposure and the outcomes.

Keywords: chronic fatigue; fibromyalgia; *Giardia lamblia*; irritable bowel syndrome; medically unexplained physical symptoms.

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Introduction

The term medically unexplained physical symptoms (MUPS) describes a range of symptoms that are not explained by measurable pathology, but are seen to occur together and lead to different symptom patterns, commonly described as syndromes [1, 2]. There is a certain overlap in criteria for the different syndromes and considerable overlap in the prevalence as patients frequently meet the criteria for several conditions [3–6]. Whether MUPS should be considered different presentations of one common condition or as distinct and different syndromes is an ongoing discussion. Many now support a view that this is a wide collection of symptoms that might have shared etiology, but can also be

divided into subgroups [6, 7]. Irritable bowel syndrome (IBS), chronic fatigue (CF) (including chronic fatigue syndrome (CFS)), and fibromyalgia are among the most studied in this group of disorders. They are associated with each other and overlap [7–10].

CFS/CF and IBS are well-known complications following infections. Previous studies have shown that long-term fatigue can complicate different infections like mononucleosis and viral meningitis, and fatigue has also been a major concern following the recent COVID-19 pandemic [11–13]. Post-infectious IBS may follow gastroenteritis caused by parasites, bacteria and viruses [14–17]. Smaller studies on fibromyalgia following infections such as mycoplasma, Lyme disease and different viruses have not provided clear support for such an association [18–22].

In 2004, a main water reservoir for the city of Bergen, Norway was contaminated with *Giardia lamblia* and an estimated 48,000 inhabitants were exposed, and about 2,500 people were treated for giardiasis [23]. Giardiasis is a rare condition in the Nordic countries and Europe, and outbreaks of this size are uncommon [24]. Three years after the outbreak, a large cohort study was set up including 1,252 patients with a confirmed infection during the outbreak and a control group. Our research group has previously reported a strong association between giardiasis and both IBS and CF three, six and ten years after the acute infection [25–27]. An association between fibromyalgia and giardiasis has not previously been explored.

Sporadic IBS and CFS/CF have often been studied together with fibromyalgia, but this triad has not been studied in the context of a preceding infection. Since we have previously documented an association between giardiasis and both IBS and CF, we wanted to investigate whether there could also be an association with fibromyalgia [26]. In 2010, new criteria for fibromyalgia formed the basis for the development of a questionnaire that with further modifications was suitable for epidemiological studies [28]. Therefore, in our ten-year follow-up we included the Norwegian version of the 2016 modified Fibromyalgia Survey Questionnaire (FSQ), a validated tool for assessment of fibromyalgia without clinical examination [29].

The main aim of this study was to investigate whether acute infection with *G. lamblia* was associated with fibromyalgia 10 years after infection and whether fibromyalgia is associated with IBS and CF in this setting.

Methods

Study design

This was a prospective cohort study set up after an outbreak of *G. lamblia* in Bergen, Norway, 2004. Laboratory-confirmed cases and a control group recruited from the same area and matched 1:2 by age and sex were followed three, six and ten years after exposure. The study population included 1,252 exposed patients and 2,504 controls. Controls reporting a physician-verified diagnosis of giardiasis in 2004 were excluded. This study is based on data from the ten-year follow-up that was restricted to participants 18 years and older in 2014 [26].

For background, we give some previously published data on the prevalence of IBS and CF here [26]. Ten years after the outbreak 43.1% (n=248) of *Giardia* exposed had IBS compared to 13.7% (n=94) among controls (p<0.001), and the prevalence of CF was 26.1% (n=153) in the *Giardia* exposed group compared to 10.5% (n=73) among controls (p<0.001) (Table 1).

Variables

The exposure in this study was identification of *G. lamblia* in stool samples during the outbreak in 2004.

The main outcome variable was fibromyalgia. Fibromyalgia was defined according to the 2016 revision of the 2010/2011 fibromyalgia diagnostic criteria [30]. In 2010, the American College of Rheumatology (ACR) approved a new set of diagnostic criteria, replacing the ones used since 1990. The new criteria increased the focus on other symptoms in addition to pain, in concordance with how the understanding of fibromyalgia has changed, and abandoned the need for an examination of tender points [28]. The questionnaire and criteria were modified in 2011 so that all items could be obtained by patient self-administration using the Fibromyalgia Survey Questionnaire (FSQ), feasible for epidemiological and clinical studies [31]. Several validation studies have been performed and the revision of the criteria in 2016 was based on the studies published up to that point. A validation study of the Norwegian version of the FSQ was published in 2020 [29].

Table 1: Characteristics, demographics and outcomes in 590 *Giardia* exposed and 696 controls 10 years after an outbreak of giardiasis in Bergen, Norway in 2004.

Characteristics		Exposed		Controls		p-Value[a]
		n	(%)	n	(%)	
Age groups, *years*	18–39	299	(50.7)	337	(48.4)	n.s.
	40–59	216	(36.6)	263	(37.8)	
	60–79	69	(11.7)	87	(12.5)	
	80–99	6	(1.0)	9	(1.3)	
Female sex		395	(66.9)	455	(65.4)	n.s.
Marital status	Single	124	(21.1)	113	(16.3)	0.040
	Married	423	(71.9)	536	(77.1)	
	Divorced/ separated	35	(6.0)	32	(4.6)	
	Widowed/ widower	6	(1.0)	14	(2.0)	
Education	Primary school	23	(3.9)	31	(4.5)	n.s.
	Secondary school	128	(21.9)	172	(25.1)	
	University	434	(74.2)	481	(70.3)	
IBS		248	(43.1)	94	(13.7)	<0.001
CF		153	(26.1)	73	(10.5)	<0.001
Fibromyalgia		49	(8.6)	21	(3.1)	<0.001

[a]Pearson's two-sided exact chi-squared test. *Abbreviations*: IBS, irritable bowel syndrome; CF, chronic fatigue; n.s., not significant, p>0.05.

The FSQ consists of two parts; the Widespread Pain Index (WPI) that assesses the number of painful body areas, and the Symptom Severity Scale (SSS) that assesses the severity of certain symptoms [30].

The WPI includes 19 body areas and participants note if they had pain in the specific area during the last week (score 0–19). The SSS consists of six items. The first three indicate symptom severity of fatigue, waking up unrefreshed and cognitive impairment during the last week on a 4-item Likert scale (score 0–3). The last three items identify the presence during the last six months of headaches, pain or cramps in the lower abdomen and depression (score 0–3). The score on the different items of the SSS are summed up to give the "SSS score" (range 0–12).

Patients have to meet three criteria for the diagnosis of fibromyalgia [30]: 1) Either WPI≥7 and SSS score≥5, or WPI 4–6 and SSS score≥9; 2) Generalized pain defined as pain in at least four out of the following five regions based on the WPI: left upper region, right upper region, left lower region, right lower region and axial region; 3) Symptoms have been generally present for at least three months.

IBS was defined according to the Rome III diagnostic criteria, which require the presence of recurrent abdominal pain or discomfort for at least three days per month in the last three months in relation to defecation or stool changes [25, 32]. Fatigue was measured by the validated Fatigue Questionnaire developed by Chalder et al. [33]. This questionnaire consists of 13 questions where 11 of these measure various aspects of physical and mental fatigue, and the last two how long and which proportion of the time symptoms have been present. CF criteria are fulfilled if there is a positive score on four or more of the 11 aspects of fatigue, and fatigue has been present for the last six months or more. The scoring and use of these questionnaires have previously been described [25].

Demographic variables included were sex (dichotomous), age (categorized in groups of 20 years, but the first group including participants from 18 years of age up to 39), marital status (four categories) and level of education (three categories) (Table 1). These were all evaluated as possible confounders by logistic regression modeling.

Statistical analyses

Participants with partially missing answers on the FSQ were allocated to a group if the answers given would unambiguously decide group affiliation.

We calculated descriptive statistics as percentages with p-values for differences between groups. The exact chi-squared test was applied to test differences in proportions. Binominal logistic regression was applied to investigate associations between fibromyalgia at ten-year follow-up, and assumed relevant or confounding variables were evaluated, i.e. *Giardia* status, IBS, CF, age, sex, marital status and education. Interactions of interest from IBS or CF on the effect of exposure status were tested in the regression model, and if not significant, they were not included in the final models. The results of these analyses are presented as odds ratio (OR) with 95% confidence intervals (CI). The level of statistical significance was set at ≤0.05. All analyses were performed in SPSS version 24.

Results

The overall response rate in the ten-year follow-up was 37.1% (1,300/3,506), with a 50.3% (592/1,176) response rate among *Giardia* exposed and 30.4% (708/2,330) among controls. Among *Giardia* exposed responders two questionnaires were returned incomplete and therefore excluded from the study, making this group consisting of 590 participants. Among controls six questionnaires returned were from individuals who had *Giardia* in 2004 and six questionnaires were incomplete, and hence a total of 12 questionnaires were excluded making the control group consist of 696 participants. There were no differences between the groups with regard to age, sex or education. However, the groups differed in marital status, as a higher proportion of controls were married or cohabitants (Table 1).

The prevalence of fibromyalgia was 8.6% (49/572) in the *Giardia* exposed group compared to 3.1% (21/673) in the control group (p<0.001). Among the *Giardia* exposed with fibromyalgia 87.0% (40/46) also had IBS and 69.4% also had CF (34/49), compared to the controls with fibromyalgia, where 50.0% (10/20) had IBS and 42.9% (9/21) had CF (p<0.001 for both) (Figure 1). Among *Giardia* exposed 4.6% (27/590) had all three conditions (fibromyalgia, IBS and CF) compared to 0.4% (3/696) in the control group (p<0.001).

Among the *Giardia* exposed with IBS 16.5% (40/242) had fibromyalgia, compared to 11.2% (10/89) among controls with IBS (p<0.001). Among the *Giardia* exposed with CF 22.8% (34/149) had fibromyalgia, compared to 12.9% (9/70) among controls with CF (p<0.001).

Table 2 shows the effects of exposure status (*Giardia* exposed vs. controls), adjusted for IBS and CF, on the OR for fibromyalgia at ten-year follow-up. Confounders evaluated were sex, age, marital status, and level of education. The unadjusted OR for having fibromyalgia was higher for *Giardia* exposed compared to controls (OR: 2.91, 95% CI: 1.72, 4.91), but adjusted for IBS and CF it was not (OR: 1.05, 95% CI: 0.57, 1.95). Regardless of exposure status, in participants without CF the OR for fibromyalgia was 6.27 times higher for participants with IBS than for those without (95% CI: 3.31, 11.91). In participants without IBS the OR for fibromyalgia was 4.80 times higher for those with CF than for those without (95% CI: 2.75, 8.37).

Discussion

To our knowledge, this is the first study to report fibromyalgia in a large cohort of patients previously exposed to a well-defined infection. We found that 10 years after an outbreak of giardiasis there was a higher prevalence of fibromyalgia in the exposed group compared to the controls. Adjusted analyses indicate that the difference was dependent on status for IBS and CF, implying that there was no association between fibromyalgia and exposure to

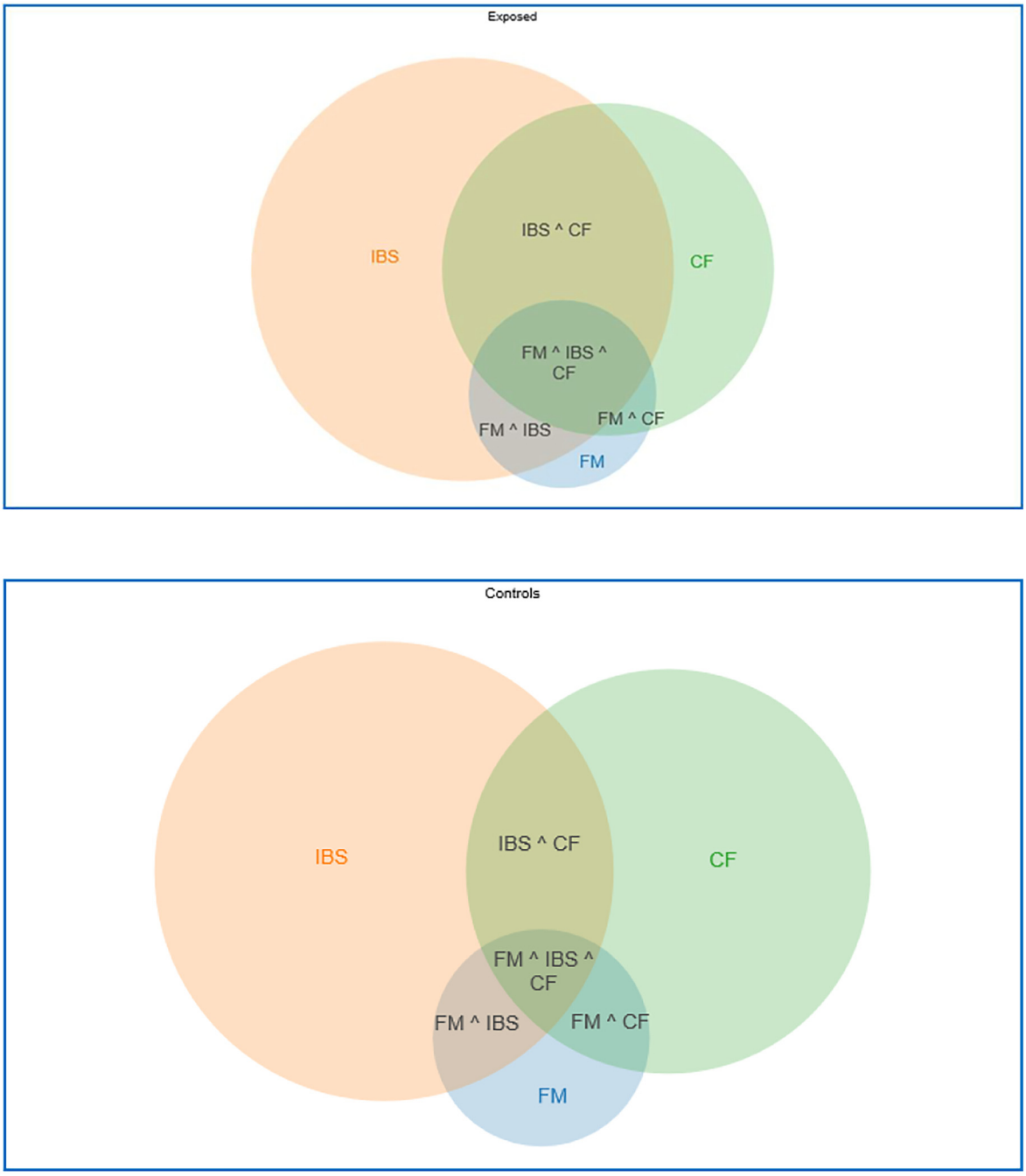

Figure 1: Venn diagram of fibromyalgia (FM), irritable bowel syndrome (IBS) and chronic fatigue (CF) in 590 *Giardia* exposed and 696 controls 10 years after the outbreak of giardiasis in Bergen, Norway in 2004.

Giardia. In the *Giardia* exposed group, there was a higher prevalence of both IBS and CF that could explain the higher prevalence of fibromyalgia in this group.

Prevalence of fibromyalgia

A meta-analysis estimated the prevalence of fibromyalgia worldwide at 1.78% in the general population, whereas European studies have found a prevalence of 2.64%, with prevalences varying from 0.29 to 11.10% [3]. This review also showed that the prevalence of fibromyalgia in more than 20 studies conducted from 1993 to 2015 based mainly on the ACR 1990 criteria was 2.32%. The ACR criteria are among the most used tools of diagnosis for studies on fibromyalgia since 1990, but has been modified since 2010. Two studies used the 2010 diagnostic criteria and one used

Table 2: Results from logistic regression analyses of fibromyalgia on *Giardia*, IBS and CF from 1,286 participants 10 years after the outbreak of giardiasis in Bergen, Norway in 2004.

Variables	Unadjusted				Adjusted (n=1,216)		
	n	OR	95% CI	p-Value	OR	95% CI	p-Value
Constant	1,286	n.r.			0.01	n.r.	n.r.
Giardia exposed/control	1,245	2.91	(1.72, 4.91)	<0.001	1.05	(0.57, 1.95)	0.873
IBS: yes/no	1,222	9.73	(5.46, 17.36)	<0.001	6.27	(3.31, 11.91)	<0.001
CF: yes/no	1,238	8.98	(5.41, 14.91)	<0.001	4.80	(2.75, 8.37)	<0.001

Abbreviations: IBS, irritable bowel syndrome; CF, chronic fatigue; OR, odds ratio; CI, confidence interval; p, p-value from likelihood ratio test; n.r., not relevant.

the modified criteria from 2011, which is obtained completely by patient self-administration. The study using the 2011 criteria found an age and sex adjusted prevalence of fibromyalgia of 6.36% in the general population in a county in Minnesota, USA, somewhat higher than in our study [34]. None of the studies reviewed were performed after 2015; hence, the 2016 fibromyalgia criteria revisions were not evaluated. In our study, fibromyalgia was defined according to the 2016 revision of the 2010/2011 fibromyalgia diagnostic criteria, which is the latest modification [30]. The European prevalence of 2.64% found in the review article above corresponds well with the prevalence of 3.1% in our control group, which is probably representative of the general population.

Different viral infections are associated with fibromyalgia [3]. Patients with chronic or carriers of inactive hepatitis B and chronic hepatitis C have reported a higher prevalence of fibromyalgia, and among patients infected with HTLV-1 there was also an association between this infection and fibromyalgia [35–38]. Studies have shown that Lyme disease may trigger fibromyalgia or widespread pain during or after active infection, but the symptoms of Lyme disease may be confused with fibromyalgia symptoms and this makes the association difficult to prove [18]. Lyme disease has effective treatment and since fibromyalgia symptoms were found to persist this can possibly be seen as a post-infectious complication. Mycoplasma infection and fibromyalgia has also been studied but it is unclear if infection can trigger or precipitate fibromyalgia [19].

Overlap of fibromyalgia, IBS and CF/CFS

Previous studies including patients with IBS have found a prevalence of fibromyalgia ranging from 12.90 to 31.60% [39–42]. These studies all based the diagnosis of fibromyalgia on physical examination. The two studies with the highest prevalence described the use of physical examination according to the 1990 ACR criteria [39, 41]. A large study from Taiwan found a higher incidence of IBS in fibromyalgia patients followed from 2000 to 2011, and fibromyalgia was associated with a 1.54 times increased risk of IBS [43].

A review article of overlap of diagnoses in patients with fibromyalgia, found that 21–80% also had CFS, and 36–60% also had IBS. Most of the underlying studies used the 1990 ACR criteria to diagnose fibromyalgia [44]. A twin study examining comorbid clinical conditions associated with CF showed a markedly higher prevalence of fibromyalgia and IBS in the fatigued compared to the non-fatigued twin. Fibromyalgia was shown in 72–77% of the fatigued twins depending on how strict the definition of fatigue was classified, compared to 0–7% among the non-fatigued twins. IBS was shown in 52–59% in the fatigued twins compared to 9–14% in the non-fatigued twins [45].

The associations between the medically unexplained conditions seen in other studies support our findings that having IBS and/or CF was an important risk factor for also having fibromyalgia. The number of respondents with fibromyalgia was small, particularly in the control group, but there was still a substantial overlap in line with previous literature on the association between these three MUPS conditions [7–10].

Comparing findings in the literature to our study is not straightforward considering the use of many different outcome-measuring tools, both questionnaires and physical examination. In addition, when examining several outcomes, some of which are rare in the general population, groups may be small and the strength of the analyses decreases. Still, our findings cohere with the literature with regard to the associations and higher prevalences of fibromyalgia when also IBS or CF is present, and patients meeting the criteria of several MUPS simultaneously [9, 22, 46].

We report prevalence of fibromyalgia at 10 years after the exposure, not incident cases after the exposure. We do not know the prevalence of fibromyalgia at baseline or in the following years up to our measuring point at 10 years. Other studies have looked at infection as a trigger for fibromyalgia, but the findings are inconsistent, where a

large review suggested that post-infectious fibromyalgia was merely relevant for subgroups of the patients [22]. In line with this, we find the higher prevalence of fibromyalgia in the exposed group to be associated with IBS and/or CF and not necessarily associated with *Giardia* exposure. These three conditions are associated, but the mechanisms are unclear. We looked at these conditions from the perspective of an infectious disease, but how this microbe might influence these associations we do not know. A previous article from our group investigating the prevalence of IBS and CF three, six and ten years after exposure, showed that close to 25% in the exposed group had persistent IBS and 14% had persistent CF, but there were also considerable fluctuations in and out of these diagnoses at the different time points [26]. This could also be the case for fibromyalgia.

Strengths and limitations

This study was a cohort study with a large number of participants. The exposed group had laboratory confirmed infection with *G. lamblia* during the outbreak, making exposure misclassification unlikely. Giardiasis is rare in Norway and the risk of the controls having been exposed to *Giardia* was small, except for during the outbreak. Accordingly, controls who reported physician-verified diagnosis of giardiasis in 2004 were excluded. The exposed group consisted of participants who contacted a physician during the outbreak which could indicate more doctor-seeking behavior in this group. This could also contribute to selection bias for patients with fibromyalgia.

We did not collect baseline data on fibromyalgia, and we do not have prevalences of fibromyalgia, IBS or CF prior to the outbreak in our study population. Higher prevalences of these conditions among the *Giardia* exposed compared to the general population can therefore not be excluded, though this is less likely to completely explain the demonstrated differences.

We used validated and well-known questionnaires to define outcomes. The FSQ includes a question on abdominal pain and a question on fatigue that can explain parts of the overlap with IBS and CF, but more symptoms are required for these diagnoses so those questions probably do not explain the overlap alone.

The response rates have declined at each point of follow-up in the exposed group and varied in the control group, making selection bias a possibility in that individuals with symptoms are more likely to respond [26]. Some degree of participation fatigue is likely. Participants might not feel the questions concerned them, it was a long time since the outbreak and this was the third time that they were asked to participate. For IBS, the prevalence decreased from 3 to 6 years and 3 to 10 years after the outbreak, but there was no change from 6 to 10 years [26]. For CF, the prevalence declined at all three measuring points. These decreases in prevalence of IBS and CF through 10 years could explain some of the decline in response rate as less participants might feel the questions concerned them.

Conclusions

We investigated the association between fibromyalgia and *G. lamblia* infection, IBS and CF. We found a higher prevalence of fibromyalgia in the *Giardia* exposed group compared to the control group. Fibromyalgia was strongly associated with IBS and CF, and the difference between the *Giardia* exposed and the control group with regards to fibromyalgia prevalence might be attributed to the high prevalence of IBS and CF among the *Giardia* exposed. This study was not designed to identify cause and effect in relation to *Giardia* exposure and the syndromes investigated.

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