Long-term complications following an outbreak of giardiasis

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«Don’t drink the water, and don’t breathe the air»

Tom Lehrer, 1965

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Bergen, April 2019

Sverre Litleskare

Olivia Søvik Litleskare, 2016

Contents

Abstract

Background

The association between certain acute infections and long-term complications is well known, with gastroenteritis and subsequent irritable bowel syndrome (IBS) as one established example. In 2004 there was a large outbreak of *Giardia lamblia* in Bergen, Norway, due to contaminated drinking-water. An estimated 5000 inhabitants fell ill with giardiasis. Before this outbreak, the knowledge on long-term complications following giardiasis was scarce.

Aims

The overall aim of the studies constituting this thesis was to investigate long-term consequences of having had a *Giardia lamblia* infection in 2004.

Methods

All three papers in this thesis are reports from a controlled cohort study. In Bergen, Norway, 1252 persons had a verified *Giardia lamblia* infection by detection of cysts in their stools during the outbreak. These were defined as the exposed population in the study and were matched 2:1 on sex and age to a control group from the Bergen area. Questionnaires were mailed to the participants three, six and ten years after the outbreak.

In paper 1 the main outcome was perceived food intolerance and its association with exposure to giardiasis three years after the outbreak. We also investigated the relation with IBS. Perceived food intolerance was measured by two unvalidated questions. IBS was defined by the Rome III criteria.

In paper 2 the main outcomes were IBS and chronic fatigue (CF). We investigated the association between giardiasis and IBS/CF ten years later, and changes in prevalence from three to ten and six to ten years. CF was defined by the Fatigue Questionnaire.

In paper 3 the main outcome was quality of life (QoL), as measured by the short-form 12 version 2. We investigated the association between giardiasis and QoL ten years later, and further, the relationship with IBS/CF.

Results

Response rates among exposed were 66%, 61% and 50% after three, six and ten years, respectively. Among controls the corresponding numbers were 35%, 36% and 30%.

Perceived food intolerance three years after the outbreak was associated with giardiasis, with an adjusted odds ratio (aOR) of 2.00 (95% confidence interval (CI) 1.65 to 2.42), as compared to the control group. Dairy products was the most frequently reported intolerance, with an aOR for exposure of 1.95 (95% CI 1.51 to 2.51). We found no interaction between exposure to giardiasis and IBS on perceived food intolerance in stratified analyses.

We found a prevalence of IBS after ten years that was 43% (248/576) among exposed and 14% (94/685) among controls (aOR 4.74; 95% CI: 3.61 to 6.23). For CF the prevalence was 26% (153/587) and 11% (73/692), respectively (aOR 3.01; 95% CI 2.22 to 4.08). There were no changes in the prevalence of IBS among the exposed from six (40%) to ten (43%) years (aOR for the change 1.03; 95% CI: 0.87 to 1.22). The prevalence of CF decreased from 31% to 26% among exposed from six to ten years (aOR for the change 0.74; 95% CI: 0.61 to 0.90).

Exposure to giardiasis was associated with a lower QoL. The mean physical component summary T-score among the exposed (51.4; 95% CI: 50.6-52.1) was 2.8 points (95% CI: −3.8 to −1.9; $P < 0.001$) lower than among controls (54.2; 95% CI: 53.7-54.8). The mean mental component summary T-score was also 2.8 points (95% CI: −3.8 to −1.9, $P < 0.001$) lower among the exposed (48.9; 95% CI: 48.2-49.6) than among controls (51.7; 95% CI: 51.1-52.4). Adjusting for IBS and CF in regression analyses resulted in no effect of *Giardia* exposure on the physical component T-score, with an estimated difference of -0.5 points (95% CI: -1.4 to 0.40; P-value: 0.28).

Corresponding numbers for the mental component summary in this model were -0.75 (95% CI: −1.7 to 0.22; P-value: 0.13).

Discussion

We found that giardiasis was associated with perceived food intolerance after three years. This is a novel finding. Stratified analyses with IBS and exposure status as independent variables and perceived food intolerance as the outcome indicated a strong association between IBS and food intolerance. The association between IBS and food intolerance is well established, and our findings were relatively consistent with findings from other studies.

The strong association between giardiasis and both IBS and CF ten years after the outbreak is surprising and unprecedented in the literature on long-term complications after gastroenteritis. The prevalence of IBS was unchanged from six to ten years, contrary to findings from studies on bacterial gastroenteritis, where post-infectious IBS has been found to subside with time.

The lower QoL among exposed than controls was statistically significant, but the clinical significance is questionable. We found no effect of exposure on QoL after adjusting for IBS and CF, indicating that these complications were the basis for the reduced QoL among the exposed.

The main methodological problems with our data were the low response rate among the exposed after ten years, and the consistently low response rates among controls, as well as a lack of baseline information about study participants. Analyses were performed to assess selection bias, and the main results from paper 2 would be significant even in the unlikely event of an extreme selection bias. A strength of all the studies was the high number of participants and the inclusion of a control group.

Conclusions

Exposure to *Giardia lamblia* was associated with long-term complications up to ten years later.

List of publications

Litleskare S, Wensaas KA, Eide GE, Hanevik K, Kahrs GE, Langeland N, Rortveit G. Perceived food intolerance and irritable bowel syndrome in a population 3 years after a giardiasis-outbreak: a historical cohort study. BMC Gastroenterol 2015;15:1:164.

Litleskare S, Rortveit G, Eide GE, Hanevik K, Langeland N, Wensaas KA. Prevalence of Irritable Bowel Syndrome and Chronic Fatigue 10 Years After Giardia Infection. Clin Gastroenterol Hepatol 2018;16:7:1064-72.

Litleskare S, Rortveit G, Eide GE, Emberland KE, Hanevik K, Langeland N, Wensaas KA. Quality of life and its association with irritable bowel syndrome and fatigue ten years after giardiasis. Neurogastroenterol Motil 2019. Epub ahead of print. doi: 10.1111/nmo.13559.

Abbreviations

aOR	Adjusted odds ratio
CF	Chronic fatigue
CFS	Chronic fatigue syndrome
CI	Confidence interval
DAG	Directed acyclic graphs
FODMAP	Fermentable oligo- di- and monosaccharides and polyols
IBS	Irritable bowel syndrome
MCS	Mental component summary
MID	Minimally important difference
MUS	Medically unexplained symptoms
OR	Odds ratio
PCS	Physical component summary
PI-IBS	Post-infectious irritable bowel syndrome
PROM	Patient reported outcome measure
QoL	Quality of life
SD	Standard deviation
SF-12	Short-form 12
SF-12v2	Short-form 12 version 2

1. Background

1.1 *Giardia lamblia*

1.1.1 Microbiology and epidemiology

Giardia lamblia (*G duodenalis* and *G intestinalis* are synonyms) is one of six species of the parasite *Giardia*. It is further divided into eight assemblages, from A-H. Only *Giardia lamblia* assemblages A and B can cause infection (giardiasis) in humans (1). This protozoan is rather ubiquitous and is the most common waterborne parasitic cause of gastroenteritis in humans worldwide. There are an estimated 280 million infections every year, and giardiasis is considered by the WHO to be a neglected disease (1). The prevalence of infection in developing countries varies from 20-30%, and in developed countries from 3-7% (2). A possible cause of the higher prevalence of giardiasis in developing countries might be lower sanitation standards. Farthing et al also discuss the possibility that healthy children in affluent areas might be more resilient towards infection than poor, underprivileged children (3). The prevalence and incidence of giardiasis as sporadic cases is probably underestimated in Norway (4), and smaller outbreaks may also go unnoticed by the authorities (5). There were 485 cases of giardiasis in Norway in 2017, giving an incidence rate of 9.22 per 100 000. 254 of the 485 cases (52.4%) were infected abroad, 130 (26.8%) in Norway, and for 101 (20.8%) patients the location was unknown (6). A meta-analysis by Hörman et al estimated the prevalence of *Giardia* cases in the asymptomatic (with no symptoms of gastroenteritis) general population to be 2.97% in the Nordic countries (Denmark, Finland, Norway and Sweden). The prevalence among cases with symptoms of gastroenteritis was 5.81% (7). Giardiasis in Norway has historically been considered mainly a problem of returned travellers and immigrants. It has not been routine for primary care doctors to request stool analysis for *Giardia* cysts when investigating gastroenteritis, nor for the laboratories to investigate for cysts without explicit requests from the clinician (4). The last years however, have seen an increase in the reported instances of giardiasis in Norway, with a provisional top in 2017. One of the main reasons for the increase is the increasing utilisation of the PCR-technique for

diagnosing giardiasis. This method is both more sensitive than microscopy of cysts (the standard method for many years), and less laborious, leading the laboratories to investigate for *Giardia* more frequently (6). Whether or not there has been an actual rise in prevalence (not just increasing diagnostic activity) is not clear. In a review from 2013, Lal et al discussed the potential effects of environmental change on the transmission of *Giardia* (8). It is difficult to predict what the sum of all the effects will be in terms of incidence of giardiasis, but it will be affected, and increasing global temperature might introduce giardiasis to areas previously too cold for it to be a significant public health-concern.

Giardia lamblia has some features that explains both why it is widespread around the globe, and why it is such a common cause of gastroenteritis. It can persist for long periods in various environments including water and food and has a high probability of infection even at low doses of ingestion (8). The cysts are resistant to some water treatment techniques, like chlorination (9), and the parasite can use both humans and

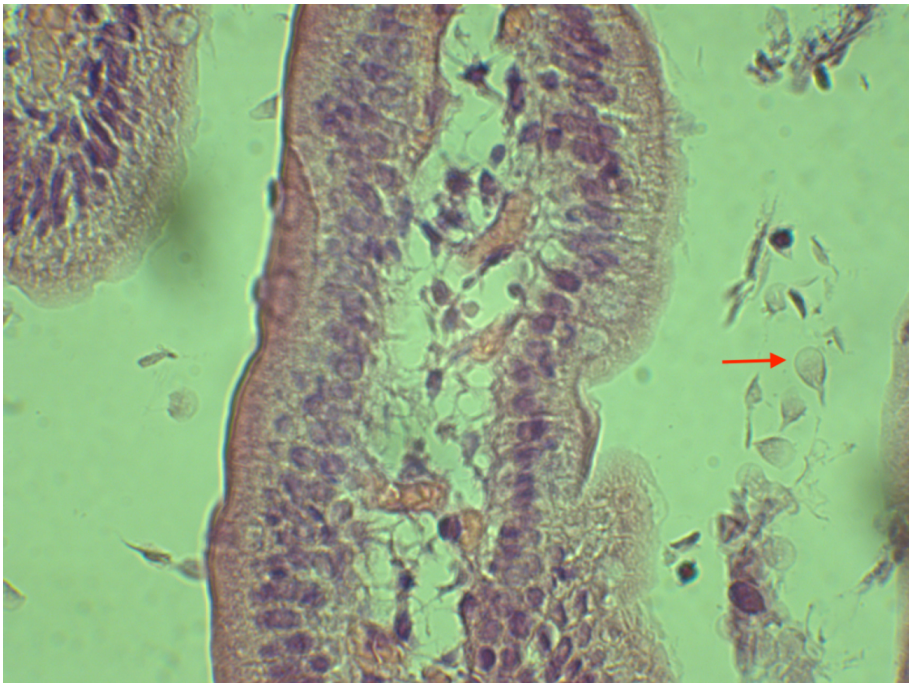

Figure 1 *Giardia lamblia in the trophozoite form (red arrow) in the duodenal mucosa of a human subject. Photo: Kurt Hanevik*

animals as reservoirs (1). The parasite has a simple life cycle with two stages. It survives outside the host as an infectious cyst. It is stimulated to enter the proliferating trophozoite form after being exposed to acid in the stomach, and bile and trypsin in the duodenum (Figure 1). It forms into a cyst again after encountering environmental changes more distal in the small intestine (10). The trophozoite form has an adhesive disc fastening it to epithelial cells in the intestinal lumen, resisting peristaltic expulsion (11). The parasite is non-invasive, but causes apoptosis to intestinal epithelial cells, increased intestinal permeability and increased hypermotility (10). The mode of transmission is through ingestion of cysts, and transmission routes (sporadic cases or outbreaks) typically include day-care centres, untreated drinking waters, treated tap water, swallowing water in swimming pools, recreational fresh-water contact, contaminated foods, person-to-person, animal contact and sexual activity (12).

1.1.2 Clinical features and treatment

Typical symptoms of acute giardiasis include diarrhoea, flatulence, bloating, abdominal pain and weight loss (10,13), but *Giardia* infections can also be asymptomatic (13). The incubation period is typically 6-15 days (10). The infection can be self-limiting, but chronic infection and re-infection also occur (2). When the symptoms are less pronounced, and perhaps only diarrhoea is present, the diagnosis can be severely delayed (13). Other causes of chronic diarrhoea are more common, and chronic giardiasis might not spring to the clinicians' mind. Metronidazole is the first line of treatment, with an efficacy ranging from 60 to 90%, and in the case of treatment failure on metronidazole monotherapy a combination of antibiotics is recommended (14).

1.1.3 Post-giardiasis complications

Giardiasis has been known to be associated with a range of both intestinal and extra-intestinal complications, some of which are related to ongoing infection and relieved after eradication of the parasite (myopathy and skin allergies). Rarer extra-intestinal complications include ocular pathologies and arthritis. Other complications are related to chronic giardiasis and can persist even long after successful eradication of the

parasite (nutritional deficiencies, failure to thrive, stunting and impaired cognitive functioning in children) (2).

In 2004 there was an outbreak of giardiasis in Bergen, the largest waterborne outbreak of any kind ever recorded in modern times in Norway (4). A total of 1252 patients had a laboratory verified diagnosis by detection of *Giardia* cysts in their stools (15). The capacity of the laboratory receiving stool samples was limited, and at a point during the outbreak patients with clinically certain giardiasis were treated with metronidazole without laboratory-verification (two letters from the municipal medical officer dated November 5th and 10th, 2004). An estimated 2500 people were treated for giardiasis during the outbreak (9). This outbreak has been extensively studied, and previously unknown long-term complications to giardiasis have been documented. Questionnaire studies of the cohort of 1252 patients with laboratory-verified giardiasis and a control group have been performed, as well as smaller questionnaire studies and clinical studies on sub-populations of patients from the outbreak. A higher prevalence among the *Giardia* exposed (as compared to a control group) of irritable bowel syndrome (IBS) and chronic fatigue (CF) has been found both 3 years (15) and 6 years (16) after the epidemic. Another study by Wensaas et al on the same cohort found a higher prevalence of functional dyspepsia, bloating, diarrhoea, nausea and foul-smelling stool/flatulence 3 years after the epidemic as compared with the control group (17). Persson et al found an increased prevalence of functional dyspepsia and overactive bladder syndrome among the exposed after six years (18), but the association between exposure and overactive bladder syndrome disappeared when correcting for IBS, functional dyspepsia and CF. Hunskar et al found that *Giardia* exposure was independently associated with daytime sleepiness and a larger sleep need (19), whereas another study found no association between asthma and atopy and development of post-infectious IBS (PI-IBS) or CF (20). Naess et al reported that the prevalence of post-infectious fatigue corresponding to a clinical entity similar to chronic fatigue syndrome (CFS) was at least eight times higher than the prevalence in two normal populations (21). The cases in that study all had laboratory verified giardiasis during the 2004 Bergen outbreak and were included between August 2005

and September 2007, after being referred to a chronic fatigue clinic at the Department of Neurology, Haukeland University Hospital. Morch et al also concluded that exposure to *Giardia lamblia* was probably associated with CFS five years later (22).

1.1.4 Possible mechanisms for the post-giardiasis complications

How a parasite that does not invade the epithelium and causes no readily apparent inflammation (23) can cause long-term complications is only partly understood. An old study from 1977 raised hypotheses about the role of the bacterial flora (in this case bacterial overgrowth in the small intestine) and deconjugated bile salts (24), and a more recent experimental study on dysbiosis and *Giardia lamblia* lend support to a role of disturbances of the microbiota (25). Clinical studies from the Bergen *Giardia* outbreak shed more light on possible mechanisms. Hanevik et al found duodenitis in patients with chronic giardiasis and abdominal complaints, that subsided with time. Some of the controls in that study (*Giardia*-infected patients where the infection was successfully treated) with similar abdominal complaints also had signs of duodenitis. The investigations in this study could, however, not establish a cause of the prolonged abdominal complaints (26). Another study by Hanevik et al found an increased CD8 T-cell count in prior *Giardia* cases with functional gastrointestinal diseases and a decreased level of natural killer cells in patients with CFS (27). This could indicate abnormal immunological function in post-infectious functional gastrointestinal diseases and CFS. Cytokines have been implicated in CFS (28), PI-IBS (23) and in giardiasis (29). Patients with CFS have been shown to have an altered gut microbiome with reduced diversity, which in turn might dysregulate parts of the immune system (30). Another study from Hanevik et al reported a differing cytokine profile between *Giardia* exposed and unexposed, but not between *Giardia* exposed with CFS and *Giardia* exposed without CFS, except for one of the measured cytokines (sCD40L) (31). Dizdar et al found that patients with PI-IBS after giardiasis had increased levels of cholecystokinin cells and reduced levels of enterochromaffin cells, as well as a lower plasma level of 5-HIAA, a metabolite of serotonin. They were compared with a control group of persons who recovered from *Giardia* with no PI-IBS (32). The finding of a lower number of enterochromaffin cells is the opposite of findings in a study by Dunlop et al (33). Another study by Dizdar et al found increased visceral

hypersensitivity in patients with PI-IBS as compared to controls without PI-IBS, but no effect on this hypersensitivity by the serotonin-antagonist ondasentron (34). Finally, Dizdar et al found prolonged alterations in duodenal mucosal lymphocytes in chronic giardiasis, with a similar pattern both among patients with post-infectious functional gastrointestinal disease-symptoms and among previous giardiasis patients without such symptoms. This pattern normalized to one similar to non-exposed healthy controls with time (35). Although some studies have found an association between small intestinal bacterial overgrowth as measured by the lactulose breath test and IBS, Morken et al could not replicate this among *Giardia* sufferers with PI-IBS (36).

To sum up, research originating from the 2004 Bergen *Giardia* outbreak has established a strong association between giardiasis exposure and IBS, CF and functional dyspepsia. Clinical studies have shown some immunological variation between various study groups, but no clear-cut cause or plausible mechanism of the prolonged symptoms have been established.

1.2 Medically unexplained symptoms

Medically unexplained symptoms (MUS), medically unexplained physical symptoms, medically unexplained physical signs/symptoms, functional disorders, functional somatic syndromes, bodily distress/stress syndrome/disorder, somatic symptom disorder, psychophysical/psychophysiological disorder, psychosomatic disorder, symptom defined illness/syndrome, somatoform disorder, complex physical symptoms, persistent physical symptoms, functional symptoms (37–39) are some of the terms that have been in use or have been proposed to be used to describe the situation when the patient has symptoms/complaints that cannot be adequately explained by evidence of organic disease (40). There has been some debate in the scientific community what to call such illnesses (37–39), and if a generic term is useful at all (37,41). Creed et al suggested ten criteria to judge the value of terms that could be used instead of MUS. They proposed that the term should: be acceptable to patients, be acceptable and useful for doctors and other health care professionals, not

reinforce dualistic thinking, be usable for patients with comorbid organic disease, have a clear core theoretical concept, facilitate multi-disciplinary treatment, have similar cross-cultural meaning, be neutral on aetiology and pathology and have a satisfactory acronym (38). Marks et al performed an online survey among healthy lay-persons investigating which of seven terms to describe MUS they deemed most appropriate. The most popular term was "Persistent Physical Symptoms," (20%) whereas "MUS" was preferred by 15%, and 24% had no particular preference (37).

It has been pointed out that many of the medical subspecialties deal with at least one functional syndrome, including IBS (gastroenterology), CFS (infectious disease) and fibromyalgia (rheumatology) (41). Wessely argued that there was considerable overlap between many of the functional somatic syndromes (or MUS) including epidemiological characteristics, proposed mechanisms, comorbidity with anxiety and depression and treatment options (41). In the same interesting exchange of opinions, White argued that this "lumping" together of illnesses supports a mind/body dualism, and that the various above-mentioned overlaps are not as convincing (and that the rates of overlap are lower in primary care), and that "splitting" of illnesses have resulted in more scientific progress than lumping (41).

The term "MUS" might be slightly misleading. Although no complete understanding of the pathogenesis of the various conditions covered by the term exist, there has been an advance in the research on the aetiology and pathogenesis of many of the conditions, as outlined for IBS and CFS in the below sections. Explanations for the patients' conditions can have a therapeutic effect in itself, even when they are incomplete (39).

Regardless of what the illnesses are called and how they are categorized, the suffering is real. The MUS conditions can affect quality of life (QoL) profoundly, as exemplified by the lower QoL among patients with IBS and CFS as compared to healthy subjects (42–46). QoL measures are important in organic diseases such as diabetes and rheumatoid arthritis, and perhaps especially in illnesses where biomarkers

to monitor illness progress or treatment effect are lacking, such as the MUS conditions.

1.3 Irritable bowel syndrome

1.3.1 Epidemiology, aetiology and pathogenesis

IBS is a functional gastrointestinal disorder, where the term "functional" refers to the lack of consistent signs of organic disease (i.e. no biomarker) (47,48). The hallmark of IBS is abdominal pain or discomfort with association to defecation and/or stool changes, with a duration of symptoms of six months or more (49). IBS is associated with decreased work productivity (50), high use of health care resources (50,51) and reduced quality of life (42,43,45,46). The global pooled prevalence of IBS is 11% (52), and a study from Norway in 2006 found the prevalence to be 8% using the Rome II criteria (53). The risk factor with the most documentation is female sex (54), with a female to male ratio of 2-2.5 to 1 (55). There is a declining incidence of IBS with increasing age (54). Other risk factors are summarized in a comprehensive review by Enck et al and include (but are not limited to) psychological factors like stress, anxiety, depression and somatization, somatic issues like gastrointestinal infection, pain and endometriosis, and social conditions (54).

Although IBS has been recognised for decades, debate still exist whether this condition is one disease or many. Differential diagnoses include the inflammatory bowel diseases, celiac disease, lactose intolerance and microscopic colitis (51). Prior to the development of adequate diagnostic tools, patients with these diseases might have been diagnosed with IBS. Many pathogenetic factors have been studied, but still no unifying theory for the pathogenesis of IBS exists. Disturbed gastrointestinal motility and visceral hypersensitivity are some of the pathophysiological factors that have been known for a while (56). Evidence of various forms of immune activation and inflammation and low-grade post-infectious inflammation is mounting, as well as a role of genes, bile-acid malabsorption and diet (56,57). The fact that the brain influences the gut has also been established in the literature (56,57), supported by evidence of the efficacy of psychological interventions on IBS-symptoms (47) and the

close relation between anxiety, depression and stress and IBS (58). More recently, the idea that the gut influences the brain has also gained interest, although the strongest evidence for this hypothesis stems from animal research. Still, there are numerous ways that the microbiota might communicate with the enteric- as well as the central nervous system (59). Also, recent longitudinal studies found that IBS precedes anxiety and depression in some patients, which might indicate that bowel disturbances could be causative factors in developing these illnesses, not just the other way around (57). The use of probiotics (microorganisms with a purported beneficial effect on health) in IBS has shown a moderate but consistent effect on relieving abdominal symptoms (60). How alterations of the human microbiota might affect human behaviour is an interesting subject for future research.

1.3.2 How to define and diagnose IBS

According to clinical guidelines and researchers on IBS, it is reasonably safe to make a diagnosis of IBS based on the Rome criteria without extensive testing, in absence of alarming features indicating organic disease (51). Despite this, a survey from 2017 found that only 32 % of general practitioners across Europe make a diagnosis of IBS based on symptoms only (without further testing). Only 36 % of general practitioners use the Rome criteria when diagnosing IBS (61). A study by Spiegel et al (2010) found that 72% of a group consisting of community gastroenterologists, general internal medicine physicians and nurse practitioners endorsed IBS as a diagnosis of exclusion (62). The reason for this discrepancy between guidelines and clinical practice remains to be resolved.

Given the lack of objective clinical symptoms or signs of IBS, there has been a continuous debate regarding how to define IBS, both in scientific studies and as a clinical diagnosis. The first attempt to find a set of criteria to define IBS was made in 1978 by Manning et al (63), who identified six symptoms based on patient responses to a questionnaire that discriminated reasonably well between IBS and organic gastrointestinal disease. These criteria were used for more than thirty years (51) and Dang et al (2012) argued that they were more valid and accurate than the subsequent Rome I-III criteria (64). The Rome I criteria were published in 1990 (65), followed by

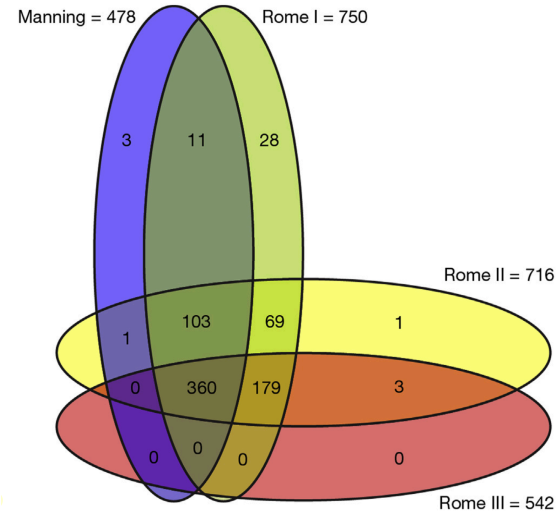

Figure 2 *Overlap between the Manning criteria and the Rome I-III criteria. With permission from A.C Ford et al*

the Rome II criteria in 1999 (66), and the Rome III criteria in 2006 (49). Similar for all four sets of criteria was the presence of abdominal pain (or discomfort in Rome I-III) and a relation to change in stool form or frequency as well as relief of pain (or discomfort) upon defecation. The required duration and frequency of the symptoms also differed somewhat between the criteria. The Manning criteria and the Rome I criteria also included criteria about passage of mucus, abdominal distension and altered passage of the stools not found in Rome II or III. Ford et al did a comprehensive validation study of the Rome III criteria in 2013 and found an overlap between the four above mentioned criteria of 47.5% (Figure 2 (67)). The Rome III criteria were found to perform only moderately in predicting an IBS-diagnosis. The reference ("gold") standard in this study for the definition of IBS was the presence of abdominal pain/discomfort associated with altered bowel habit and an absence of organic gastrointestinal disease (including negative endoscopies as indicated) (67).

In 2016 the Rome IV criteria were released, and the main differences from the Rome III criteria regarding IBS were 1) the removal of the term "discomfort" from the definition, 2) the presence of pain at least once a week as opposed to three times per month and 3) abdominal pain that is *related* to defecation as opposed to *improved* with defecation (68). The new criteria were validated before release, and a prevalence of IBS of 5.7% was found in the reference population using the Rome IV criteria as compared to 10.7% using Rome III. Point 2 above made the largest impact in lowering the prevalence of IBS (69). In the project from which this thesis springs out, we used

the Rome III criteria to define IBS. According to these criteria, IBS can be further classified into diarrhoea or constipation predominant, mixed or unsubtyped (49).

PI-IBS is defined using the same criteria as for sporadic IBS and hence in most respects is clinically similar to sporadic IBS, although Dunlop et al found that diarrhoea was more common among PI-IBS individuals than among individuals with IBS of unknown origin. They also had less psychiatric illness, and an increased number of serotonin-containing enterochromaffin-cells (33). IBS and PI-IBS patients are managed similarly in the clinic (70).

1.4 Chronic fatigue

Definitions of fatigue vary, and the prevalence will obviously vary according to the strictness of the criteria used to measure fatigue and the population under study. Fatigue as a symptom, even when considered chronic (duration six months or longer), was highly prevalent both in the general Norwegian population (11%) (71) and in a Dutch general population (31%) (72). Both studies were performed in a representative population. The Norwegian study used the Fatigue Questionnaire and was performed in 1996 (71). How chronic fatigue was defined in the Dutch population was not entirely clear, but it was described as a fatigue lasting longer than six months but not meeting the CDC-94 criteria for CFS. It was performed in 2003 (72). In USA, 24% of patients attending primary care considered fatigue a "major problem" (73). CF accompany various diseases, both somatic and psychiatric (71).

CF is an important part of the more strictly defined CFS. CFS is a clinical diagnosis, which depends on exclusion of relevant causes for fatigue. Various criteria exist, and some are also used in questionnaire studies without clinical assessment (74). One estimate based on the CDC-1994/Fukuda criteria found a prevalence of self-assessed CFS to be 3.3% whereas clinically assessed CFS had a prevalence of 0.76% (74). A study on fatigue in the Dutch general population found that there were similarities in the lifestyles among patients classified by different definitions of fatigue (short-term fatigue, CF and CFS according to CDC-94 criteria) and hypothesised that these

different forms of fatigue were not necessarily different types of disorders, but different manifestations on a continuum of fatigue (72).

The pathogenesis of CFS is far from completely understood, but there is accumulating evidence for immunological disturbances associated with the condition. Whether these disturbances are the cause or the effect of the conditions is not yet established (75). A recent study by Naviaux et al found a metabolic response among CFS-sufferers that was homogenous and statistically robust (76). Infections such as the Epstein-Barr virus, Q fever and viral meningitis have been associated with an increased risk of CFS (77).

Fatigue is also a common symptom in chronic gastrointestinal disease (78,79), and previous studies from our group has found considerable overlap between IBS and CF among patients with previous giardiasis (15,16).

1.5 Food hypersensitivity

Food hypersensitivity means that the patient has an adverse reaction to food. Hypersensitivities can be divided into food allergies that are immunologic in origin (IgE or non-IgE mediated, or a mixed type) and food intolerances, that are non-immunologic (80). This classification misses celiac disease, that although it is of immunologic origin, is not normally classified as an allergy (81).

1.5.1 Food allergy

The true prevalence of food allergies is uncertain, and estimates vary according to definitions, populations and methodology, and self-reports probably overestimate the prevalence (82). It is more common in preschool children (4-7%) than among adults (1-2%) (81). The most common allergies in children are to cow's milk, egg, peanut, soy, tree nut and shellfish, and for adults it is peanut, tree nut and seafood (81). There is no clear evidence of an association between food allergy and IBS (83).

Ideally, an IgE-mediated food allergy is diagnosed based on anamnestic information about adverse reactions to the culprit food, followed by remission upon removal of the

food from the diet, and confirmation by a positive serum IgE test and maybe also a positive skin prick test (81).

1.5.2 Celiac disease

Celiac disease is an immune-mediated reaction to gluten, affecting about 1.5% of the population in Northern Europe. Simona et al proposes that four out of the following five criteria should be met to diagnose celiac disease: anamnestic information compatible with the disease, presence of serum-autoantibodies, positivity for HLA-DQ2 or DQ8, duodenal biopsy and symptom-improvement when adhering to a gluten free diet (84).

1.5.3 Food intolerance

Up to 15-20% of the general population report food intolerance. These intolerances can be divided by purported origin into: 1) pharmacologically mediated intolerances (salicylates, amines, glutamates, caffeine), 2) intolerances based on enzyme or transport defects (lactase dehydrogenase deficiency), and 3) unknown origin, including the incompletely understood non-celiac gluten sensitivity (85).

Hydrogen/methane breath tests assessing carbohydrate malabsorption exist, but their clinical usefulness in detecting intolerance to various groups of carbohydrates is questionable. Apart from these tests, there are no validated objective tests to verify the various food intolerances (85), which can be frustrating for both patients and health care providers (86).

1.5.3.1 Food intolerance in IBS

As many as 70% of individuals with IBS report that different foodstuffs influence their symptoms (87), and 90% of persons with self-reported food hypersensitivity had IBS in one study (86). A few studies have mapped the foodstuffs patients with IBS report to cause symptoms, and some of the culprit foods include: milk, milks products, wheat products, caffeine, certain meat, cabbage, onion, peas, beans, hot spices, fried foods and smoked products (88). The NICE Guideline for IBS recommends restricting the intake of coffee, tea, alcohol and fizzy drinks, reducing the amount of high-fibre food and resistant starch and limiting the intake of fruits. Patients with diarrhoea should not

ingest sorbitol. If these more general advice fail, patients can try out single food avoidance and/or exclusion diets, including the low FODMAP- diet, as advised by a healthcare professional with expertise in dietary management (89). FODMAP is an acronym for fermentable oligo- di- and monosaccharides and polyols, and these are a group of poorly absorbed carbohydrates (90). The low FODMAP-diet has gained a lot of interest, and there is an accumulating amount of evidence for its efficacy in relieving IBS-symptoms in the short-term, whereas long-term effect on microbiota and gastrointestinal functioning is uncertain (85,91).

1.5.3.2 Food intolerance in chronic fatigue

The research on food intolerance and fatigue is scarce. One recent review found 17 studies investigating various dietary and nutrition supplements as treatment for CFS-symptoms and concluded that there was not enough evidence to recommend modified diets for such symptoms (92). IBS is a common comorbidity of CFS, and when IBS is present, the dietary advice given for IBS might apply. Berstad el at found that 85% of 84 patients referred to tertiary care for self-attributed food hypersensitivity had fatigue (not CFS). Notably, all but one of the same 84 patients also had IBS (93). Preliminary results from our research group indicate an independent association between perceived food intolerance and CF, even when adjusting for IBS-status (unpublished data).

1.6 Quality of life

Patient reported outcome measures (PROM) are self-report instruments used to assess the patient's perspective on their own health status and treatment (94,95). PROM measures can be generic or disease-specific. Generic PROM instruments assess health concepts that are relevant to most patient groups and can be used to compare PROM between different conditions and healthy persons but will miss some points that are of

special interest to specific diseases. These are better assessed by disease-specific instruments, which in turn cannot be used to compare different conditions (95).

Constructs measured by PROMs include QoL, health-related QoL, health status, wellbeing (i.e. measures of depression and anxiety), patient satisfaction and symptoms and functioning (95).

The short-form 36 (SF-36) is a PROM that is widely used, and was found to perform better than other similar instruments on many of the properties measured in a review by Bryan et al (96). The short-form has also been simplified to a shorter version, the short-form 12 (SF-12) while retaining good validity (97). It has been cross-validated in nine European countries including Norway (98). The SF-12 is referred to in the user manual as a measure of "health status" (99), however, Meadows et al state that health status is not synonymous with QoL (95). Studies utilizing the SF-36 or SF-12 nevertheless refer to this measure as assessing health-related quality of life (42), and the homepage of the RAND corporation, which distribute the SF-36, classify the SF-12 and SF-36 as QoL measures (100).

The last search for literature for this thesis was performed on the 31th of March 2019.

2. Aims of the present study

This thesis is part of a bigger project investigating long-term complications after the *Giardia lamblia* outbreak in Bergen, Norway 2004.

The aims of the study comprising this thesis were:

Paper 1: To compare the prevalence of perceived food intolerance among *Giardia* exposed as compared to a control group, and to explore how this was related to the presence of irritable bowel syndrome in the two groups. We also aimed to investigate the associations between exposure status and content of fermentable oligo- di- and monosaccharides and polyols in the reported foods.

Paper 2: To estimate the prevalence and odds ratio of irritable bowel syndrome and chronic fatigue ten years after acute giardiasis as compared to a control group. The secondary aims were to investigate changes in prevalence from three to ten and from six to ten years and to estimate incidence, recovery, and persistence of these conditions.

Paper 3: To evaluate the association between giardiasis and quality of life ten years after the outbreak, as compared to a control group. The secondary aim was to assess how quality of life related to irritable bowel syndrome and chronic fatigue in the exposed and the control group.

3. Materials and methods

3.1 Setting and design

In the autumn of 2004 one of the main drinking water reservoirs of Bergen Municipality was contaminated by *Giardia lamblia* cysts. There were almost 50 000 individuals registered as recipients of drinking water from this source, in addition to facilities typical of a medium sized city (hotels, restaurants, offices, etc) (9). Around 5 000-6 000 persons were infected with *Giardia lamblia* cysts, according to an external report investigating the outbreak (101). During the period of the outbreak 1252 patients were identified who also had *Giardia lamblia* cysts detected in their stools. *Giardia lamblia* is not endemic in Norway and hence this was an outbreak of giardiasis in a population that was previously largely unexposed to the parasite. It has sometimes been referred to as a "natural experiment," and an observational prospective study with a control group was designed to investigate the clinical consequences of the outbreak. The inclusion of a control group was important, because many of the complications we planned to investigate were known to have a high prevalence in the normal population. Data for all 3 papers were collected by mailed questionnaires. For paper 1 data from follow-up three years after the outbreak were used. For papers 2 and 3 data from follow-ups at three, six and ten years after the outbreak were used.

3.2 Participants

The 1252 patients identified with *Giardia cysts* in their stools constituted the exposed group in all three papers (Figure 3). A control group was established by sampling individuals from Bergen matched on sex and age. Two controls were selected for each of the exposed, resulting in a control group of 2504 individuals. As the controls were from the same area as the outbreak took place, a question was included to assess whether the controls had been exposed to *Giardia* infection. Controls who self-reported a doctor-verified diagnosis of giardiasis in 2004 were excluded. This makes misclassification of exposure status less likely. Misclassification of *Giardia* exposed

as controls would bias the results toward the null hypothesis, or, in other words, increase the likelihood of a type II error: not finding an association where one exists. Due to a low response rate among controls at the three-year follow-up (862/2504; 34%), questionnaires were sent to an additional 1094 control persons six months later. The response rate among these controls was even lower (271/1080; 25%). The additional control group was included in paper 1, but not in papers 2 and 3. Papers 2 and 3 included data from follow-ups three, six and ten years after the outbreak, and for the two latter follow-ups no extra controls other than the 2504 original participants were contacted by mail.

For the ten-year follow-up we excluded children under 18 before questionnaires were sent. For papers 2 and 3, children who were under 11 and 14 at the three- and six-year follow-ups (who had answered the questionnaires), respectively, were therefore removed before the analyses. We discussed whether to remove all children below 18 for the three- and six-year follow-ups as well, but this would lead to more missing cases in the longitudinal analyses. Persons who were 11 or more in 2007 or 14 or more in 2010 would be 18 in 2015 and hence eligible for participation.

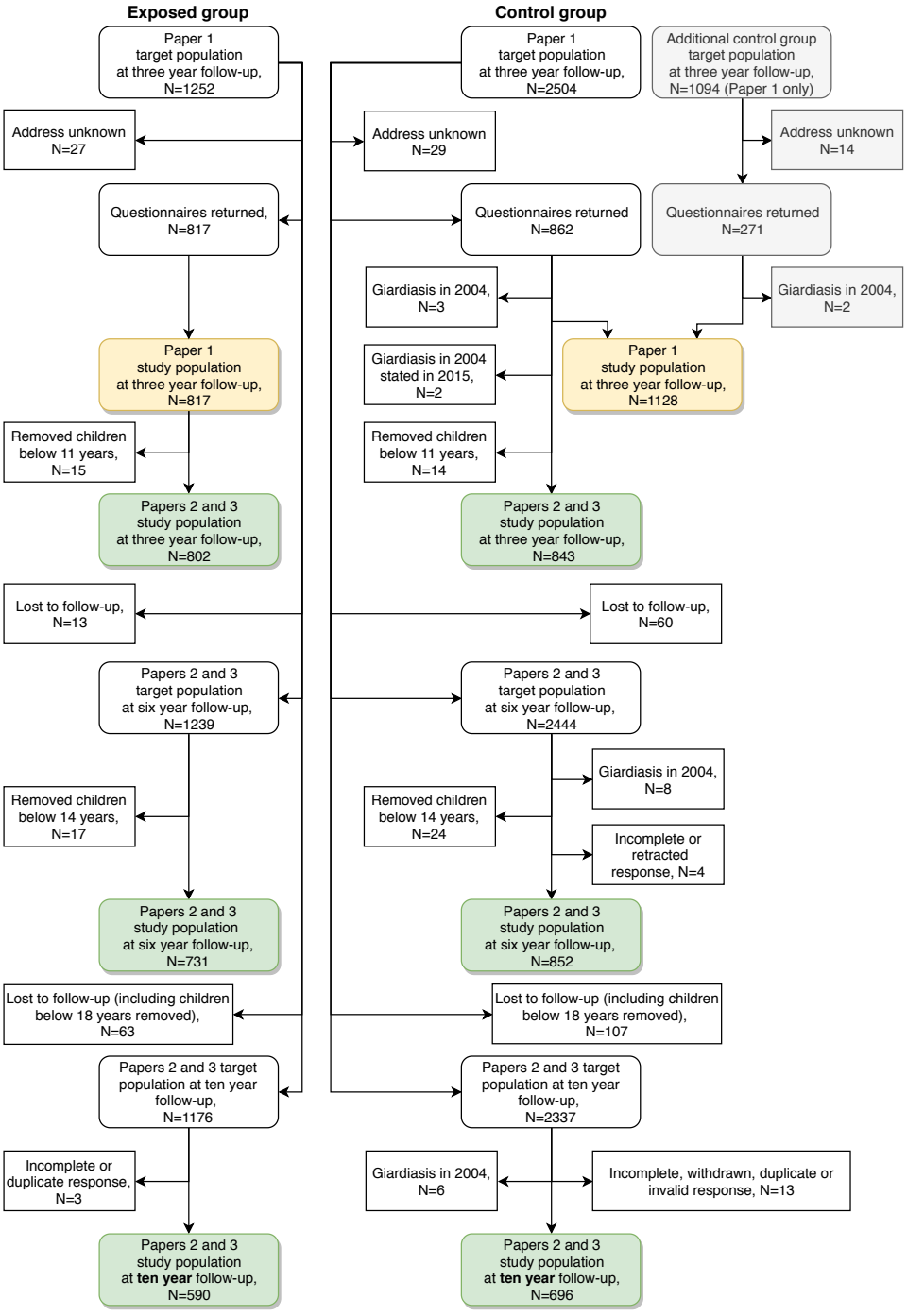

Figure 3 *Flow-chart of the participants available for study at follow-ups three, six and ten years after giardiasis in Bergen 2004*

3.3 The questionnaires and the variables

The content of the questionnaires was chosen based on clinical observations from doctors during the outbreak, findings from studies of the outbreak and existing literature. Table 1 shows the topics investigated. The six uppermost topics in bold font are the ones further investigated in papers 1-3. The questionnaires can be found in Appendices 2-4.

Table 1 Overview of content of the questionnaires sent to participants three, six and ten years after the Bergen 2004 *Giardia lamblia* outbreak

	Years after *Giardia* infection		
Theme	**3**	**6**	**10**
Demographic variables	x	x	x
Known *Giardia* infection (controls only)	x	x	x
Irritable bowel syndrome	x	x	x
Chronic fatigue	x	x	x
Food intolerance	x		
Health-related quality of life			x
Pregnant at time of answering questionnaire	x	x	x
Consent to linkage of response to registry data	x	x	x
Dyspepsia	x	x	
Milk intolerance	x	x	
Sleep	x	x	
Asthma, allergy	x	x	
Status as student in 2004	x	x	
Abdominal complaints prior to giardiasis (exposed only)	x		
Consent to linkage of response to clinical tests	x		
Questions about information and treatment	x		
Urinary tract symptoms		x	
Fibromyalgia			x

The six uppermost themes (presented in **bold** type) are used in the studies comprising this thesis

3.3.1 Exposure variable

Giardia lamblia infection was the exposure in all three papers. The exposure variable was dichotomic with the categories exposed or control.

3.3.2 The demographic variables

Sex and age were obtained from the participants' social security number and were considered as confounders for papers 1 and 2. Although obtained after the outbreak,

these variables should be considered baseline information as they are given by birth. Marital status (4 levels), level of education (3 levels) and source of income (recorded with 8 levels, categorized to 4 levels) were recorded at each of the three follow-ups, and were considered as confounders in all papers. Status as a student was recorded after three and six years, and only considered as a confounder in paper 1.

3.3.3 Irritable bowel syndrome

Studies from one and two years after the outbreak found a high prevalence of abdominal complaints after giardiasis (102,103), but with unvalidated questions used in the assessment of gastrointestinal symptoms. It was therefore decided to use the Rome III criteria (49) to define IBS in the later follow-ups. These were not validated at the time of the planning of this study, but they were based on the Rome II criteria, which had been used in prior research on IBS. Also, a working team of renowned researchers in the field of functional bowel disorders recommended their usage in research on IBS (49). The Rome III criteria were later validated (in 2013) in a study performed in Canada by Ford et al (67).

IBS is defined according to the Rome III criteria as an abdominal pain/discomfort present for at least 2-3 days of the last three months, with symptom onset six months before the response. At least two out of three additional criteria must also be met: 1) improvement of pain/discomfort with defecation; 2) change in frequency of stool at onset; 3) change in form (appearance) of stool associated with onset (49). We also defined "severe IBS" as IBS that limited daily activities at least often. IBS subtyping was performed according to the Rome III criteria also, sub-dividing the participants with IBS into IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed (IBS-M), and unsubtyped (IBS-U).

IBS was investigated as an interacting factor in paper 1, as an outcome in paper 2 and as a mediating agent and interacting factor in paper 3.

3.3.4 Chronic fatigue

Several patients complained of fatigue in the period after the outbreak. Morch et al found a high prevalence of fatigue at 41% based on one question in a study carried out

two years after the outbreak. It was therefore decided to investigate this further with a validated fatigue questionnaire, and the Fatigue Questionnaire was chosen (104), partly because it had been used in a Norwegian general population previously (71). The scoring of the Fatigue Questionnaire has been described in detail in paper 2 (105). In short, responses on a Likert-type scale were dichotomized, and a total dichotomized score of four or more constituted a case of CF, if the symptoms had lasted six months or more. Severe CF was defined as CF with a total fatigue score of 23 or more.

CF was investigated as an outcome in paper 2 and as a mediating agent and interacting factor in paper 3.

3.3.5 Eight-level exposure variable

For paper 3 we constructed an eight-level variable by combining the dichotomous variables exposure status (exposed/control), IBS (yes/no), CF (yes/no). The reference category in regression analyses was "neither condition among controls." The remaining categories where: "neither condition among exposed," "IBS-only among controls", "IBS-only among exposed", "CF-only among controls", "CF-only among exposed", "IBS and CF among controls", and "IBS and CF among exposed".

3.3.6 Food intolerance

Four questions about food were included in the questionnaire sent to the respondents after three years. The first two were regarding milk in particular and were not included in the analyses in paper 1. The latter two were included. The first of these was an unvalidated question regarding ailments from the bowels in relation to foodstuffs, phrased as follows (translated from Norwegian): "Do certain types of food give you abdominal symptoms?" Possible answers were: None, light, moderate and severe. The second question was an open-ended question: "If you react (to food), to what kind is that?" The answers to this question were categorized based on categories from the literature (88,106–108), and some were made by the research group. Every category was accounted for in a codebook.

Perceived food intolerance, both in general, and according to specific food categories, was the main outcome of paper 1.

3.3.7 Health-related quality of life

At the outset of the sub-studies of this thesis, the association between exposure to *Giardia* and IBS and CF had already been established (15,16). IBS (42,43,45,46) and CFS (44) has been associated with a reduced QoL in previous studies, but the impact of giardiasis on the QoL and, further, the relation with IBS and CF, was unknown. The symptom-burden associated with IBS can range from mild (not even leading to contact with the healthcare system) to severe (disability), depending on the population investigated (i.e. surveys from the normal population, investigations among patients in tertiary clinics, etc). It was therefore important to assess how QoL was affected in this particular setting.

The SF-12 version 2 (SF-12v2) was chosen as it is generic, widely used and takes a relatively short time to answer for the respondents. The 12 questions assess eight domains of health related QoL, that are further compiled to two measures of QoL, the physical component summary (PCS) score and the mental component summary (MCS) score. Both scores have a theoretical range of 0-100. It is scored by an algorithm provided by a commercially available computer programme (99), where a normal population from USA inn 2009 is used as a reference. This population has a mean PCS and MCS of 50 with a standard deviation (SD) of 10. The calibration of the PCS and MCS against an US norm makes comparisons across populations more relevant.

PCS and MCS were the main outcomes for paper 3.

3.4 Analyses and statistical methods

3.4.1 Directed acyclic graphs

We did not have unbiased baseline information about our respondents, other than age and sex. The demographic variables marital status, level of education and source of income are measured at the same times as the outcomes, at follow-ups three, six and ten years after the outbreak. Directed acyclic graphs (DAG) can aid the planning of the analyses, by giving a visual representation of the relationships between the study

variables. Some of the newer R packages can also use code generated from the creation of the DAGs directly in R to test if the DAG is consistent with the dataset (109). We only used DAGs as a visual aid for our studies. Figure 4 depicts various DAG-models of causality for our study of QoL after ten years (paper 3). Model 1 is the most complete (and complex), including unobserved variables depicted as grey circles, indicating the lack of baseline information. Model 2 is one of the working models we used in the analyses, where marital status, level of education and source of income were treated as confounders. Under this model age and sex were excluded as the statistical method accounted for the matching of the subjects. Model 3 depicts a scenario where IBS an CF are considered mediators of the effect of exposure on QoL. None of the models gives full justice to the real-world setting, and all models are approximations.

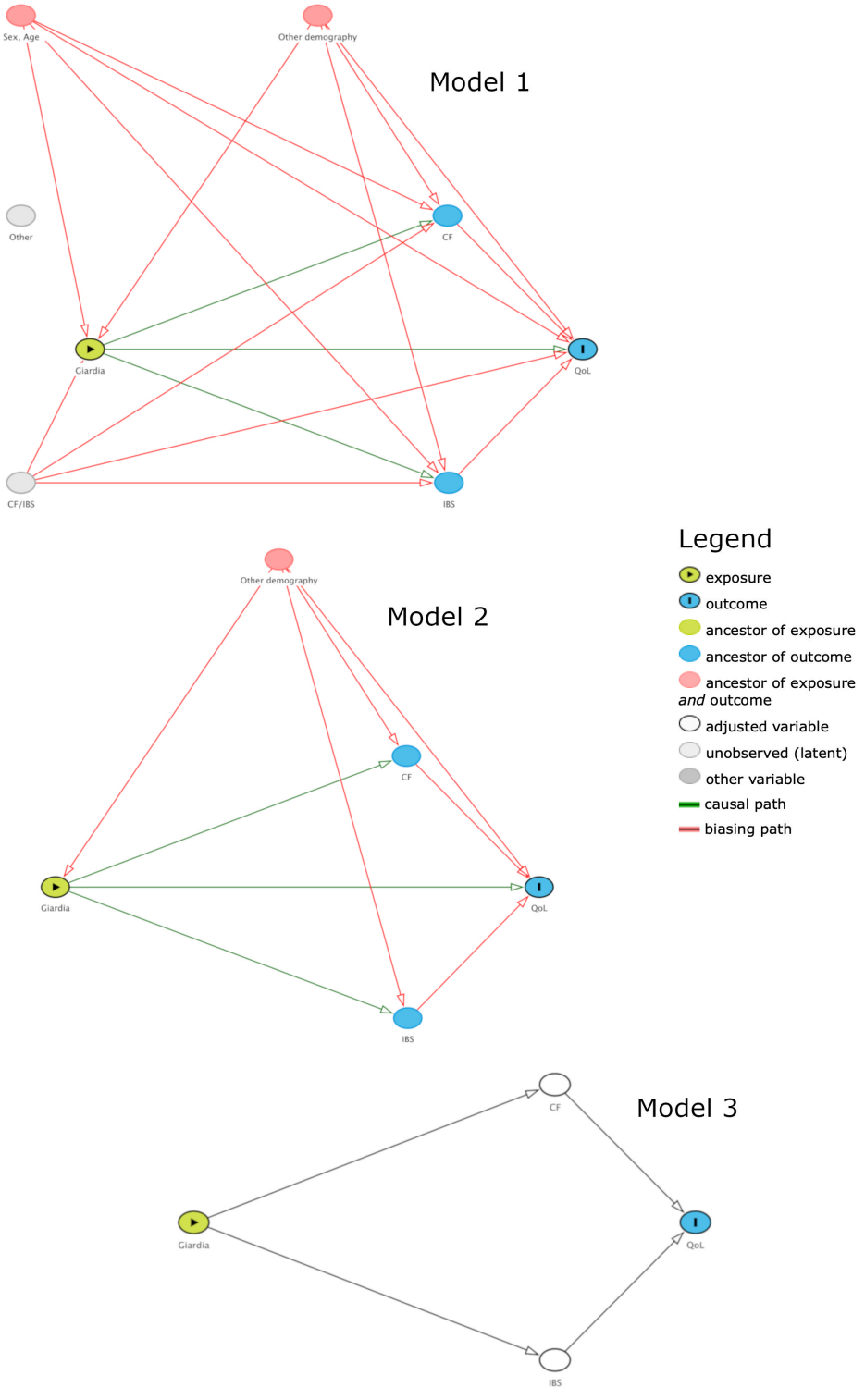

Figure 4 *Directed acyclic graphs of different models of causality for variables in a study ten years after a 2004 Giardia lamblia outbreak in Bergen, Norway*

3.4.2 Analyses

Descriptive statistics were calculated as percentage or mean for papers 1-3, and for some of the data in paper 3 we also calculated the SD and 95% confidence intervals (CI).

Differences between proportions were tested with Pearson's chi square exact 2-sided test for all categorical variables in paper 1. In papers 2 and 3 we used Pearson's chi square exact 2-sided test for categorical multilevel outcomes and Fisher's exact 2-sided mid-p test for binary outcomes (110). Student's t-test was used for analyses of age as a continuous variable in papers 1 and 2. Since the exposure and control group were matched for sex and age, testing for differences for these variables could be considered superfluous, and hence were not performed in paper 3.

In paper 1 and 2 we used standard logistic regression analyses for the outcomes perceived food intolerance (paper 1) and IBS and CF (paper 2). For the changes in prevalence over time for IBS and CF in paper 2, we used generalised estimating equations as this regression-method accounts for the correlation between repeated measures and the matched design. For the main outcomes in paper 3, we used mixed models, another regression method that accounts for the matching of the subjects.

Interactions were investigated using the Breslow-Day test for homogeneity of the odds ratios (OR), and with the appropriate regression method when applicable. Confounding was investigated, and adjusted for when necessary, in regression models.

All tests were two-sided with the level of statistical significance set to 0.05. The analyses were done using IBM SPSS Statistics for Windows, version 22 (paper 1), version 24 (paper 2) and version 25 (paper 3). Sankey diagrams used for Figure 1 in paper 2 were plotted using R (111) with the package sankeyD3 (112). The causal models in Figure 4 in this thesis were made using the web application DAGgity (109).

3.5 Ethical approval

Paper 1 was 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). Papers 2 and 3 were approved by the Regional Committee for Ethics in Medical Research (ref.no. 2014/1372).

4. Results

The response rates in the three papers are presented in Table 2. The same cohort has been studied at three follow-ups. There are some differences between paper 1 and papers 2 and 3 for the three-year follow-up data, because of the exclusion of the second control group and children aged 10 and below for papers 2 and 3. The response rate among the exposed had declined at each follow-up, whereas the control group had a similar response rate at three and six years but dropped at ten years. These changes have not been tested for statistical significance.

Table 2 Response rate per year in exposed and control cohort three, six and ten years after a *Giardia lamblia* outbreak in Bergen, Norway, 2004

	Years after giardiasis											
	Three years (paper 1)			Three years (papers 2 and 3)			Six years (papers 2 and 3)			Ten years (papers 2 and 3)		
Group	n	N	%	n	N	%	n	N	%	n	N	%
Exposed	817	1252	65.3	802	1218	65.8	731	1205	60.7	592	1176	50.3
Control	1128	3598	31.4	843	2436	34.6	852	2378	35.8	708	2330	30.4

4.1 Paper 1

The prevalence of perceived food intolerance was high both among the exposed (63.9%) and among controls (47.6%). The adjusted odds ratio (aOR) for perceived food intolerance for the exposed group was 2.00 with 95% CI: 1.65 to 2.42, as compared to the control group (Table 3). Perceived intolerance for dairy products was the most frequently reported intolerance, with an aOR for the exposed of 1.95 (95% CI: 1.51 to 2.51). Perceived intolerance for fatty foods, vegetables, fruit, cereals and alcohol was also significantly higher in the exposed group. The groups did not differ in perceived intolerance to spicy foods, coffee or soda. In stratified analyses the association between exposure to giardiasis and perceived food intolerance was significant within the no-IBS group (aOR 1.36; 95% CI: 1.07 to 1.72), whereas within the IBS group it was not (aOR 1.25; 95% CI 0.78 to 2.01). The difference was small, and the Breslow-Day test for homogeneity of the OR was not significant. Perceived intolerance for high FODMAP foods (aOR 1.91; 95% CI: 1.57 to 2.33) and low

FODMAP foods (aOR 1.55; 95% CI: 1.26 to 1.92) were both associated with exposure status.

A wide variety of foods were mentioned, and the categories made were (number of respondents who mentioned foods in the category in parenthesis): Dairy products (292), spicy foods (256), vegetables (232), cereals (227), milk (163), fruit (120), alcohol (109), meats (93), coffee (91), fatty foods (75), wheat (73), unclassified (46), sweets (45), soda (40), sugar (33), dinners (29), gravy/dressing (28), beer (26), chocolate (25), juice (25), eggs (23), baked goods (22), fish (21), shellfish (21), yeast products (18), smoked food (17), nuts (17), processed food (15), tomato/tomato products (15), fruit juice (14), gluten (11), fibre (8), tea (8), salted food (8), soy (3).

Table 3 Perceived food intolerance according to food categories and FODMAP content in 817 *Giardia* exposed and 1128 controls three years after an outbreak of giardiasis in Bergen, Norway, 2004. (This table is a modified version of the tables from the original article).

	Exposed N = 817		**Controls N =1128**		**Adjusted[c]**	
Category	**n**	**%**	**n**	**%**	**OR[d]**	**95% CI**
Yes to question on food intolerance in general[a]	488	63.9[a]	524	47.6[a]	**2.00**	**1.65 to 2.42**
Food categories[b]						
Dairy products	163	20.0	129	11.4	**1.95**	**1.51 to 2.51**
Spicy foods	119	14.6	137	12.1	1.25	0.96 to 1.63
Fatty foods	48	5.9	27	2.4	**2.63**	**1.62 to 4.26**
Vegetables	118	14.4	114	10.1	**1.56**	**1.18 to 2.06**
Fruit	75	9.2	45	4.0	**2.45**	**1.67 to 3.60**
Cereals	128	15.7	99	8.8	**1.98**	**1.49 to 2.62**
Alcohol	66	8.1	43	3.8	**2.29**	**1.54 to 3.40**
Coffee	39	4.8	52	4.6	1.05	0.68 to 1.61
Soda	17	2.1	23	2.0	1.03	0.55 to 1.94
FODMAP content[e]						
High FODMAP	308	37.7	277	24.6	**1.91**	**1.57 to 2.33**
Low FODMAP	230	28.2	231	20.5	**1.55**	**1.26 to 1.92**

Abbreviations: FODMAP: fermentable oligo- di- and monosaccharides and polyols; IBS: irritable bowel syndrome; CI: confidence interval; OR: Odds ratio.
a Question A, with total n = 764 for exposed and n = 1100 for controls;
b Question B: "If you react (to food), to what kind is that?";
c Adjusted for sex and age;
d Statistically significant ORs are presented in **bold** font;
e Assumed FODMAP content of the response(s) to question B

4.2 Paper 2

The prevalence of IBS (Figure 5) after ten years was 43% (248/576) among exposed and 14% (94/685) among controls (aOR 4.74; 95% CI: 3.61 to 6.23). For CF the prevalence was 26% (153/587) and 11% (73/692), respectively (aOR 3.01; 95% CI:

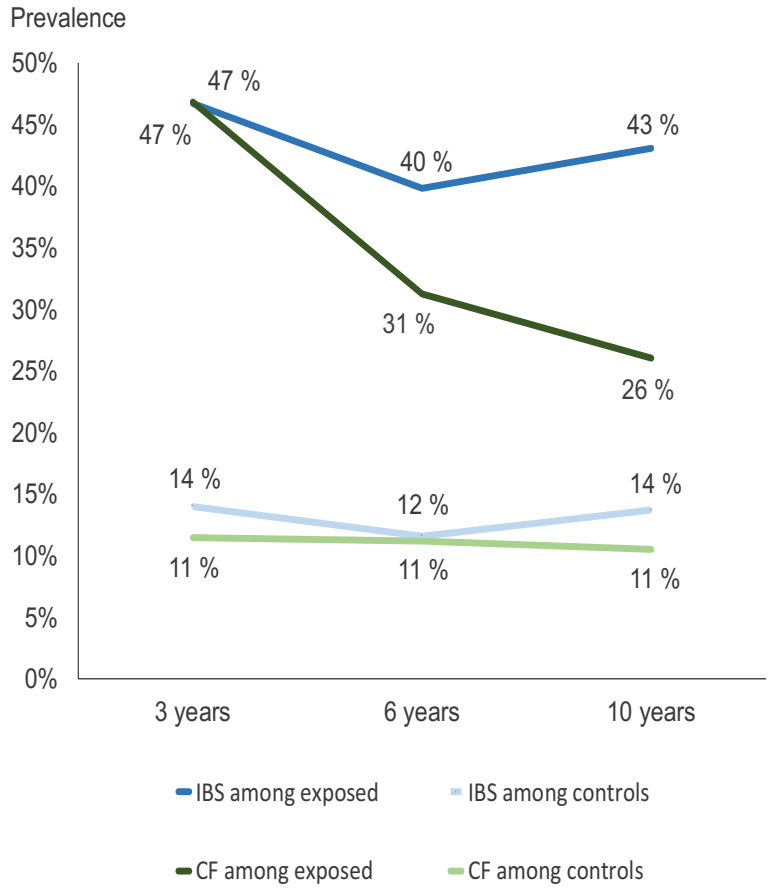

Figure 5 *Changes in prevalence of irritable bowel syndrome (IBS) and chronic fatigue (CF) three, six and ten years after a Giardia lamblia outbreak in Bergen, Norway 2004*

2.22 to 4.08). The prevalence of IBS among the exposed was unchanged from six (40%) to ten (43%) years (aOR for the change 1.03; 95% CI: 0.87 to 1.22). There was a decrease in prevalence both from three (47%) to ten years (aOR for the change 0.75; 95% CI: 0.63 to 0.90) and from three to six years (aOR for the change 0.73; 95% CI: 0.62-0.86). The prevalence of CF decreased from 31% to 26% among exposed from

six to ten years (aOR for the change 0.74; 95% CI: 0.61 to 0.90). The prevalence also decreased from three (47%) to ten years (aOR for the change 0.40; 95% CI: 0.33–0.48), and from three to six years (aOR for the change of 0.53; 95% CI: 0.46–0.62). There were no changes in prevalence of IBS or CF for any of the periods among controls. The results for the prevalence and time changes from three to six years have been published previously by Hanevik et al (16), but were calculated anew for our study, because of a slightly changed study population. The results were nonetheless similar.

We also investigated the different possible trajectories of IBS and CF among the subgroups with valid answers at all years and found that there was a considerable flow in and out of the two conditions over the years. Persistent IBS (IBS that was present at all three follow-ups) was strongly associated with exposure to Giardia, with an aOR of 19.3 (95% CI: 8.3 to 44.7). Stability of the IBS subtype was low.

4.3 Paper 3

QoL was measured with two scales, one for physical QoL (PCS), and one for mental QoL (MCS). The mean PCS T-score for the entire cohort regardless of group was 52.9 (SD: 8.7) and for MCS it was 50.4 (SD: 9.1).

The mean PCS T-score among exposed (51.4; 95% CI: 50.6-52.1) was 2.8 T-score points (95% CI: −3.8 to −1.9; $P < 0.001$) lower than among controls (54.2; 95% CI: 53.7-54.8). The mean MCS T-score was also 2.8 T-score points (95% CI: −3.8 to −1.9, $P < 0.001$) lower among the exposed (48.9; 95% CI: 48.2-49.6) than among the controls (51.7; 95% CI: 51.1-52.4).

"Neither condition among controls" was the reference category in regression analyses on an eight-level categorical variable constructed from the three dichotomous variables IBS (yes/no), CF (yes/no) and status as exposed or control. The reference category had the highest QoL for both PCS and MCS, with mean T-scores of 55.4 (95% CI: 54.9-55.9) and 53.4 (95% CI: 52.8-54.0), respectively. The category "Neither condition among exposed" had the same PCS as the reference category. All other categories had a lower QoL than the reference categories, both for PCS and

MCS. The lowest PCS was found for “IBS and CF among exposed,” with a PCS of 42.2, an estimated 13.1 T-score points lower than the reference group (95% CI for estimated difference: -14.8 to –11.5). The lowest MCS was found for “CF-only among controls,” with an MCS of 41.1, an estimated 12.3 T-score points lower than the reference group (95% CI for estimated difference: -14.7 to -10.0).

We performed regression analyses with status (as exposed or control), IBS (yes/no) and CF (yes/no) after ten years as independent variables and PCS as the outcome. When adjusting for IBS and CF there was no effect of exposure on the PCS T-score, with an estimated difference in T-score of -0.5 (95% CI: -1.4 to 0.40; P-value: 0.28). We found the same for MCS, with an estimated difference in T-score of -0.75 (95% CI: −1.7 to 0.22; P-value: 0.13).

We found an interaction between CF and exposure status on QoL. Exposed with CF had a PCS 9.2 T-score points lower than exposed without CF (95% CI for difference: -10.7 to -7.7), whereas the corresponding number for controls was 4.7 T-score points lower (95% CI for difference: -6.6 to -2.7; P-value for interaction <0.001). For MCS we found the opposite: The reduction in MCS due to CF was larger among controls (estimated T-score difference -10.9; 95% CI: -12.9 to -8.9) than exposed (estimated T-score difference -8.0; 95% CI: -9.6 to -6.4; P-value for interaction =0.027).

There were some post-publication errors in papers 1 and 2, please see Appendix 1 "Errors in papers 1 and 2".

5. Discussion

The main findings of this thesis were that acute infection with the parasite *Giardia lamblia* was associated with long-term complications and consequences such as perceived food intolerance after three years, IBS and CF after ten years, and a reduced QoL after ten years. The association between giardiasis and QoL was explained by the presence of IBS and CF.

5.1 Methodological considerations

All three sub-studies in this thesis were based on a controlled cohort study. We have described the design of the sub-study in paper 1 as a historical cohort study, and papers 2 and 3 as prospective studies. The classification of observational studies as prospective or historical (or retrospective) is not necessarily straight forward or even agreed upon in the scientific community. Based on an interesting discussion of the terms by Klebanoff et al (113), the sub-studies included in this thesis may be termed ambidirectional (meaning that they are both historical and prospective), and the prospective elements are more dominating the more follow-ups that are included in the given study.

5.1.1 The lack of baseline data

This was an observational study, with the cohorts established after the outbreak. We therefore did not have information about the respondents from before the outbreak. This includes a lack of information on all of the variables in the study (except for sex and age), including the outcome variables, which is a drawback when assessing the different causal roles of the various variables. We still believe that this design gives reliable and valid data with trustworthy results. Two designs would theoretically be more robust but were not applicable: 1) An observational study assessing all the inhabitants in an area at a randomly assigned "baseline" and then waiting to see if an outbreak of interest occurs. This would be both expensive and probably unethical and might never give results. 2) A proper randomized controlled trial emulating an

outbreak would also, of course, be wildly unethical. Consequently, the current design is the best available in the real world.

It would also be possible to use the respondents' social security number and assess retrospective pre-outbreak data from the national database for reimbursement claims (which includes doctor- and patient identification-number, date and time for the contact, and diagnoses for the contact). One such study has been planned by members of the research group and may shed some light on the respondents' pre-outbreak vulnerabilities. However, this strategy has methodological constraints as well.

5.1.2 Selection bias

Selection bias refers to bias introduced by factors influencing study participation and how the subjects are selected (114). The exposed in our studies are selected compared to all *Giardia* exposed in the population, in terms of help-seeking behaviour, which resulted in a test for *Giardia lamblia* cysts in their stools. If people with pre-existing IBS or CF would be more prone to seek medical help for acute giardiasis, we have a situation where our results would be biased away from the null-hypothesis of no association between exposure and the outcomes (IBS and CF). One could also speculate, however, that people with pre-existing IBS would be less inclined to seek medical help during giardiasis, as they could interpret their symptoms as a worsening of their known condition. This would bias our results towards the null. The sum of these and other selection biases are unknown. A few studies have examined this question. A study from Italy hypothesised based on their findings that rather than giardiasis causing IBS, it makes pre-existing IBS evident by making the symptoms apparent (115). This was a small study, so the results should be treated with caution. Parry et al found that pre-existing IBS was more frequent among cases presenting with gastroenteritis than among a group of controls. A study by Wensaas et al (102) from the Bergen *Giardia* outbreak included a question on whether the respondents had abdominal complaints at present that were absent before the outbreak, but answers to this question correlated poorly with information from medical records in another study by the same authors (116). In sum, some studies from this outbreak have assessed the association between pre-existing abdominal complaints and post-infectious

complaints, and although there were some indications of such an association (26,116), only a subset of patients were investigated. The question used to detect pre-outbreak abdominal complaints was unvalidated and prone to recall bias, and we conclude that the evidence for an association between pre-existing abdominal complaints and post-infectious complaints is not clear. Even if people with pre-existing abdominal complaints were more likely to consult a doctor during gastroenteritis, this is not likely to explain all of the effect of exposure on the outcome of IBS but would overestimate the effect somewhat.

Attrition bias is a form of selection bias due to loss of participants, both from nonresponse and drop-out. The response rates at our follow-ups are low but acceptable among the exposed (66-50%) and somewhat low among controls (36-30%). If the reasons for nonresponse are related to the outcome, bias can occur. We therefore conducted various analyses in paper 2 trying to assess selection bias (supplementary material in paper 2). We found that there was an association between having IBS among the exposed at follow-ups three and six years after the outbreak, and responding after ten years, but the effect was small. There was also a negative association between having CF after three years among controls and answering after ten years. These results could imply that the results at ten years were biased away from the null hypothesis because of nonresponse. We therefore conducted a sensitivity analysis where we assumed that all nonresponders among the exposed would be categorized as no IBS, and nonresponders in the control group would have the same IBS prevalence as responders. Even in this unlikely scenario, we found a positive association between giardiasis and IBS ten years later, and the same was also true for CF. We therefore conclude that the associations between exposure to *Giardia* and IBS and CF are both robust. The prevalence of IBS in the control group at the three follow-ups reported in paper 2 ranged from 12-14%, comparable to a population survey in Denmark of persons aged 18-50 utilizing the Rome III criteria, which found a prevalence of 16% (117). This could suggest that selection bias did not influence the prevalence much and further supports our results.

5.1.3 Choosing the appropriate statistical method

Sometimes the choice of method can have profound effects on the effect measure. We used chi square statistics from cross-tabulations and standard logistic regression, as well as generalised estimating equations and mixed models (special forms of regression analyses that account for matching of respondents and repeated measures). One could argue that we should have used a method that accounted for the matching in all analyses, and that we should have used only one of those. Table 4 shows that at least for the main outcomes of paper 2, the choice of method had a very small effect on the results. We also performed analyses with both generalised estimating equations and mixed models for some of the outcomes in paper 3, without significant changes of the results (data not shown).

Table 4 Unadjusted odds ratios for irritable bowel syndrome and chronic fatigue ten years after a 2004 *Giardia* outbreak in Bergen, Norway, utilizing different statistical methods

	Irritable bowel syndrome		Chronic fatigue	
Statistical method	OR	95% CI	OR	95% CI
Pearson's chi square exact 2-sided	4.75	3.62 to 6.25	2.99	2.20 to 4.05
Standard logistic regression	4.75	3.62 to 6.25	2.99	2.20 to 4.05
Generalised estimating equations[a]	4.77	3.65 to 6.25	3.00	2.21 to 4.06
Mixed models[a]	4.78	3.65 to 6.25	3.02	2.23 to 4.09

a) These two methods take the matching of the subjects into account. Both were set up with an unstructured matrix.

5.2 Interpretation

In the studies comprising this thesis we found that *Giardia lamblia* infection was associated with several long-term complications and consequences. We found an association between exposure and perceived food intolerance three years later, exposure and IBS/CF ten years later, and a reduced quality of life ten years later.

5.2.1 Giardiasis as a cause of the associated complications

There are no universal and objective criteria to identify a certain cause- and effect relationship. Causality is normally referred to as more or less probable, and definitive proof is impossible in empirical science, although our best tentative working models can have practical applications (114). In 1965, Sir Bradford Hill proposed a set of nine

considerations he argued could be useful in identifying causal associations. These considerations were *strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence* and *analogy*. Except for the necessity of the cause to precede the effect (temporality), none of them are sufficient or necessary in themselves to propose causality. Also, the development of more sophisticated methods in research and integrations of these methods has altered the way we use and interpret these considerations (118). Yet, they are still relevant, and perhaps especially so for our rather classical epidemiologic design. The following section will consider our findings in light of the Bradford Hill causal considerations, with the main attention on IBS.

Considering the *strength* of an association is not necessarily straight forward. Also, a causal relationship can exist even if the association is weak, and a strong association can be a result of confounding (114). The association between exposure and the main outcomes of IBS and CF after ten years should be considered strong, based on relatively large ORs, low p-value and confounding for measured variables adjusted for when appropriate. The association between perceived food intolerance and exposure is somewhat lower in terms of the size of the OR, but not weak. It should be noted that a mere eyeballing of the size of ORs should be done with knowledge that arbitrary factors (like the number of explanatory variables in the model) other than the strength of the relationship per se influences its magnitude (119). The association between exposure and QoL is strong in terms of statistical significance, but the difference of 2.8 T-score points between the exposed and controls for both PCS and MCS might not be clinically significant. Regarding IBS, our findings are *consistent* with findings from other studies, that an association between *Giardia lamblia* and IBS exists (120–122), and also between gastroenteritis caused by various agents (protozoa, bacteria, viruses) and IBS (123–128).

I have previously discussed how the lack of baseline data is a concern for our study. This is also a threat to the issue of *temporality*. We know that *Giardia lamblia* infection preceded our assessments of the prevalence of IBS at the follow-ups, but we did not have access to the cohorts' prevalence of IBS prior to the outbreak. However,

the most important issue to consider regarding temporality is whether the putative cause cannot (under any circumstance) precede the effect (114), which is not the case in our study.

Although the prevalence of IBS after this outbreak is surprisingly high compared to other studies on post-infectious IBS (126), the findings are still *plausible,* based on prior knowledge from the field. Also, we have not found any research in direct conflict with our findings, which supports the *coherence* criterion.

Qin et al systematically reviewed the evidence from animal models of post-infectious IBS and found that PI-IBS could be experimentally induced in rats and mice by infecting them with various bacteria and parasites (129). None of the reviewed articles included *Giardia lamblia* as an agent, but this nevertheless constitutes *experimental evidence* that infective gastroenteritis can cause IBS. By use of *analogy,* it is plausible that animal models with *Giardia lamblia* would yield similar results.

The only causal considerations clearly not met or readily assessed by our studies are *specificity* (IBS and CF can have many causes, and *Giardia* infection can lead to various complications), and *biologic gradient* (we did not assess the "dose" of *Giardia* infection for the exposed cohort in any way).

A consideration not directly related to the Bradford Hill criteria but still relevant for assessing causality concerns the results in paper 2. We found that the prevalence of IBS and CF was unchanged through all follow-ups in the control group. In the exposed group, the prevalence of IBS falls from three to six years and then plateaus, whereas the prevalence of CF falls at all three follow-ups. This indicates that the *Giardia* infection was something that happened in the lives of the exposed, that at least changed the trajectories of those two conditions.

5.2.2 Our main findings in relation to the literature

5.2.2.1 Paper 1

Our main finding of an association between exposure to *Giardia* and perceived food intolerance long after eradication of the parasite has to the best of my knowledge not

been thoroughly explored previously and is a novel one. When stratifying according to IBS status, there was no association between giardiasis and perceived food intolerance in the IBS-group. In the no IBS group, there was a weak association between giardiasis and perceived food intolerance. The Breslow-Day test for interaction was, however, negative. One implication of this finding could be that IBS was a mediator for the relationship between giardiasis and food intolerance. However, we did not perform further analyses to elucidate this relationship. Also, IBS and perceived food intolerance was measured at the same time, so the relationship could also be the opposite: perceived food intolerance could be a mediator for the relationship between giardiasis and IBS. Alternatively, IBS and perceived food intolerance are both in part effects of giardiasis and developed concomitantly. It is safe to conclude that there is a strong relationship between IBS and perceived food intolerance, a finding in line with the existing literature (83,106,107,130).

Nutrition intake is very difficult to measure accurately in questionnaires (131). Predefined checklists of foods probably overestimate the prevalence of those particular foods (132). Similarly, there are methodological issues related to the categorization and analysis of responses to an open-ended question. There is always a risk of misclassification. In this study, every category was accounted for in a codebook. The codebook was also checked by a nutritionist. Ideally, the classification should have been done by two investigators independently and checked for concordance, but we did not have the resources for this. If a respondent did not mention a foodstuff for a given category, this was coded as a “no” for that particular category. There is uncertainty related to the validity of this, but also, this was the only meaningful way to make categories available for comparisons between the two study groups. The probability of misclassification should be similar among the exposed and the controls, and hence is a non-differential misclassification. This further means that the misclassification will result in inferences about prevalence more uncertain than the inferences about associations between the exposure and the outcome.

Like many other studies on IBS and perceived food intolerance (107,130,133), respondents in this study mentioned a wide range of foods as causing abdominal

complaints. Interestingly, only 11 participants answered "gluten" as an offending food (although 227 answered "cereals," many of which might contain gluten). With the recent focus on gluten in the media and the medical/research community, also in persons without celiac disease, these numbers would probably be higher if our survey was performed today. Based on the inherent problems with findings from observational studies on nutrition, our data do not justify a conclusion that these are the only offending foods, or even that they necessarily are the real culprits. Neither do our results warrant the formulation of concrete dietary advice. We conclude that food in general is an important issue for respondents with IBS and that the spectre of possible offending foods is broad. Since the publication of paper 1 there have been some more randomized controlled trials investigating the efficacy of the low FODMAP-diet in relieving symptoms among patients with IBS. In a review by Altobelli et al, the low-FODMAP diet was found to be superior to standard dietary advice. There is still a need for high quality clinical diet intervention studies for IBS in primary care.

5.2.2.2 Paper 2

Our main finding from this study was a high prevalence of IBS and CF among the *Giardia* exposed and a strong association between giardiasis and IBS/CF ten years after the acute infection. Persistence of IBS and CF (as measured by IBS or CF at all three follow-ups) was strongly associated with giardiasis. The stability among respondents (both in the exposed and the control group) of IBS/CF was low through the three follow-ups, as was the stability of the IBS-subtype.

The still high prevalence of IBS at 43% (compared to 7-36% for PI-IBS after epidemics in one review (126)) found after ten years in our exposed cohort has several possible explanations. Selection bias has been discussed previously, and even in a worst-case scenario (accounting for maximum selection bias) the prevalence in our cohort would be rather high. Direct comparison of prevalence with other studies is complicated by how IBS is defined. In the above-mentioned review all the studies reviewed had utilized Rome I or II criteria, while Rome III was used in our study. The Rome III criteria had recently been published when the first survey for the cohort used

in this thesis was being planned. Before this, and for some time after, studies in Norway and worldwide often utilized the Rome II criteria, and in 2016 the Rome IV criteria were published (69). Hence, the amount of studies available for direct comparison using the same criteria are scarce, both on IBS in general, and especially concerning PI-IBS. A review from 2011 by Schwille-Kiuntke on post-infectious IBS found no studies using the Rome III criteria (126), and a later systematic review of post-infectious IBS after traveller's diarrhoea found two studies using these criteria (124). Andresen et al followed a cohort of patients suffering from a severe infection with Shiga-like toxin-producing *Escherichia coli* (128) in 2011 and utilized the Rome III criteria. They found that the prevalence of IBS increased from 9.8% before the infection, to 25.3% 12 months after.

The population under study might also affect the prevalence. The exposed in our cohort were recruited by the fact that they had consulted a doctor for abdominal complaints. The doctor sent stool samples to the laboratory, that later turned out to be positive for *Giardia lamblia*. The infection struck the citizens of Bergen in a random manner, and apart from the unknown importance of health-care seeking behaviour in this group. Interestingly, the reported prevalence of PI-IBS after travellers' diarrhoea is lower than that after epidemics. The authors of a meta-analysis on PI-IBS after travellers' diarrhoea (124) discussed the possibilities that 1) travellers are younger and perhaps more resilient than the average epidemic-stricken population and 2) respondents after a large outbreak might interact in ways that lead to over-reporting of symptoms. There might also be legal/financial implications of the reporting of symptoms after an outbreak caused by contaminated drinking water. In the 2004 Bergen outbreak, the Municipality of Bergen assumed responsibility for the outbreak in 2005 and gave compensation for economic losses of the affected. Hence, such considerations might play a minor role for the responses three, six or even ten years after the outbreak.

Several agents have been implicated in PI-IBS (23) including bacteria: *Campylobacter jejuni, Salmonella enterica, Shigella sonnei, Escherichia coli, Clostridium difficile* (134); viruses: Norovirus; and parasites: *Giardia lamblia*. A recent study found that

the parasite *Cryptosporidium hominis* was associated with diarrhoea and abdominal pain (PI-IBS was not an outcome) as well as fatigue (among other symptoms) up to two years after the infection (135). The prevalence and persistence of PI-IBS vary according to the agent. Bacteria have been associated with longer-lasting PI-IBS than viruses (23), and our research indicates that *Giardia lamblia* might be associated with longer-lasting symptoms and a stronger association to PI-IBS than bacteria.

5.2.2.3 Paper 3

The main findings in this study was a lower QoL among *Giardia lamblia* exposed persons ten years after the infection, as compared to a control group. The effect of the exposure was mediated by IBS and CF.

Both the PCS and MCS were 2.8 T-score points lower among the exposed than among controls. These differences were both statistically significant at the $P < 0.001$ level. They were, however, slightly lower than the threshold for clinically significant differences according to the cut-off for a "minimally important difference" (MID) between groups of 3 T-score points (approximately 1/3 of the SD (10) from the 2009 US population norm) (99). MID pertains to the smallest difference in score between groups that has some clinically meaningful effect perceivable to the individual. A reduction in PCS score of 3 T-score points was associated with an increased risk of being unable to work, losing one's job or being hospitalized the following year. A reduction in MCS of 3 T-score points was associated with a 40% increased risk of depression (99). The difference between the exposed and controls in our paper for PCS and MCS is close to this threshold, and even though it is not within the MID, it would be false to assume that this translates to no meaningful loss of QoL for any of the respondents. At least for PCS, a threshold of 2 T-score points for the MID has been discussed, and there is an inherent uncertainty in defining cut-off for any scale measure, especially perhaps, for a PROM-measure.

We used a calculated 1/3 of the SD from the Norwegian population to estimate the upper and lower bounds of a MID, which because of SDs smaller than 10 for the means, yielded MIDs smaller than 3. The choice of a MID of 3 T-score points might

have been more correct and simpler to present, but this minor difference would not have altered the inferences presented below. Both the exposed and controls had a PCS and an MCS that was within or above that of a Norwegian population measured in an SF-12 1998 European validation study (98). When stratifying the respondents to the eight-level variable (exposure status x IBS x CF), only two out of eight groups had a PCS T-score lower than 1/3 of an SD of the mean from the Norwegian comparison population. These groups were "CF only among exposed" and "IBS and CF among exposed." For MCS, four out of eight groups had such a low T-score, and these were "CF only among exposed," "CF only among controls," "IBS and CF among exposed" and "IBS and CF among controls."

We used the recommended scoring-algorithm for the SF-12v2, automated by computer software. Our scores were calculated using the 2009 US norms as a reference. Although not a primary aim of the study, we compared the findings in our study to a Norwegian norm that was based on the SF-12 (not v2) in a population from 1998. The SF12v2 scoring manual states that although the SF12-v2 is an improvement over the SF-12, scores from studies utilizing the SF-12v2 are comparable to the scores from utilizing the SF-12, and from studies utilizing SF36. Comparability is increased if the studies have used the standard scoring algorithm, as we did.

Comparing our results to the Norwegian norm and to other studies utilizing the Short-form, was done by mere eyeballing, without statistical analysis. Comparing our results to others was not a main objective of the study, and a subjective assessment was considered accurate enough to place our findings in a broader context. Even though the various versions of the Short-form are comparable across studies, the population under study will vary, and thus the differences in QoL between studies is not necessarily caused by the impact of the different conditions measured alone.

How the relationship between the exposure and QoL was affected by IBS and CF was a secondary aim of paper 3. Inferences about causality between IBS/CF and QoL, about interactions between exposure and IBS/CF on QoL and about IBS and CF as mediators for the effects of exposure on QoL are made problematic by the fact that

IBS, CF and QoL were measured at the same time, after ten years. We therefore included analyses on IBS and CF after three and six years and the relationship with exposure and QoL as well. The results from these analyses were largely similar to the main findings, with a few exceptions. The most notable exception was the fact that the interesting interaction between exposure and CF on QoL was only found for CF measured after ten years. This could be a power problem, as there were fewer cases who answered both at three and ten years or six and ten years than at ten years independently. However, there is also a chance that this was a spurious finding.

We used a classic approach to mediation analysis, where we compared two regression models, one with and one without adjusting for the mediators IBS and CF. Richiardi et al (136) have pointed out that under certain circumstances, this method can introduce bias. One circumstance is when mediator-outcome confounding exists. We did not find such confounding by the demographic variables assessed (marital status, level of education and source of income) on the mediation. Another situation is when there is an exposure-mediator interaction. We found an interaction between exposure and CF (one of the mediators) on both PCS and MCS, and this may be a source of bias in the mediation analysis. Methods to estimate effect of the mediation in the presence of exposure-mediator interaction exist (136), but we did not apply these. The final circumstance in which the classical approach to mediator analyses can introduce bias, is when the mediator-outcome confounding might be affected by the exposure. We discussed this briefly in paper 3. The demographic variables mentioned above are measured after the exposure, and hence can be affected by it. When assessing the relationship between the confounders and exposure, we found that only marital status differed significantly between the groups. For the relationship between the confounders and the outcome (PCS/MCS) there was an association for all the confounders (data not shown). We have not used methods to adjust for this. To sum up, we have used a classical approach to mediation analyses, prone to bias. We used methods to adjust for the mediator-outcome confounding, but not for the exposure-mediator interaction nor for the situation where the mediator-outcome might be

affected by the exposure. Regarding the latter two, we present enough information so that at least the avid epidemiologists will be aware of the possible biases.

5.2.3 Mechanisms for the development of post-infectious complications

I have argued in the above for a causative role of *Giardia lamblia* in the development of the post-infectious complications, with most of the emphasis on IBS. IBS is thought of as a multifactorial disease, and gastroenteritis is one of many contributing factors (54). Deary et al described the cognitive behavioural model of MUS in a narrative review (137). The model has a structure of predisposing, precipitating and perpetuating factors. Applying this model to our findings, *Giardia lamblia* is a precipitating factor. As mentioned before, we do not have access to baseline information, and hence possible predisposing factors in our cohorts are largely unknown. Known risk factors (that can be thought of as predisposing factors) for developing post-infectious IBS are female sex, younger age and premorbid psychological conditions (54). Wensaas et al concluded that sex was not a strong risk factor for IBS after giardiasis in a three-year follow-up of the Bergen *Giardia* cohort (15). In the six-year follow-up by Hanevik et al, sex was a risk factor for IBS among controls, but not among the exposed (16). In paper 2, sex was not a risk factor for IBS among the exposed after ten years. Neuroticism has been associated with the development of IBS after bacterial gastroenteritis in other studies (138), but this was not replicated in a small group of patients (N=134) with giardiasis after the Bergen outbreak by Wensaas et al in a one-year follow-up (102). We did not assess premorbid psychological factors in the follow-up studies included in this thesis.

As mentioned in the first paragraph of this thesis, studies from the Bergen *Giardia* research group have investigated alterations in the bowels both in giardiasis and in PI-IBS as compared to various controls, and found some changes associated with both giardiasis and with PI-IBS. Several other studies have also investigated and found physiological bowel-alterations in PI-IBS (23,139). The fact that there are physiologic changes associated with PI-IBS does not in any way imply that psychological factors are unimportant as either predisposing, precipitating or perpetuating factors, as psychological stress also can lead to physiological changes. According to the cognitive

behavioural of MUS, psychological factors such as sensitization (heightened response to a stimulus because of a prior exposure to them), attention, attribution, beliefs and behaviour are important in the perpetuation of MUS illness (137). Even more thought-provoking, Wildman et al raised the possibility that repeated measurements of fatigue in a Q fever outbreak cohort could cause or perpetuate some of the fatigue measured (140). Schwille-Kiuntke also discussed this as a possible phenomenon for the assessment of functional symptoms in general (124). Although not likely to explain all of the post-infectious complaints in our exposed cohort, similar mechanisms cannot be completely ruled out.

6. Conclusion

Through three sub-studies based on mailed questionnaires to a *Giardia lamblia* exposed group of patients and a control group, we have found that giardiasis is associated with long-term complications up to ten years after the acute infection. Giardiasis was associated with perceived food intolerance three years later, and IBS and CF and reduced QoL ten years later.

There are some important limitations addressed in this thesis. However, there is reason to believe that the design of the study mitigates most of the shortcomings. The associations between giardiasis and the outcomes are strong and the findings reliable, particularly for IBS and CF.

The research presented in this thesis furthers our understanding regarding the aetiology of MUS diseases and might provide clinicians with helpful explanations for patients' ailments.

7. Further research

Future research on large outbreaks should have routines for collecting as valid baseline information as soon as possible, to strengthen the conclusions of the studies. A possible research angle for new studies could be to try hindering the transition from the acute infectious/inflammatory phase to the phase with long-term complications.

Source of data

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PAPERS 1-3

Including supplementary material

PAPER 1

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RESEARCH ARTICLE Open Access

Perceived food intolerance and irritable bowel syndrome in a population 3 years after a giardiasis-outbreak: a historical cohort study

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Abstract

Background: Studies have shown an increased prevalence of irritable bowel syndrome (IBS) after acute gastroenteritis. Food as a precipitating and perpetuating factor in IBS has gained recent interest, but food intolerance following gastroenteritis is less investigated. The aims of this study were firstly, to compare perceived food intolerance in a group previously exposed to *Giardia lamblia* with a control group; secondly, to explore the relation with IBS status; and thirdly, to investigate associations with content of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) in foods reported.

Methods: This is a historical cohort study with mailed questionnaire to 1252 *Giardia* exposed and a control cohort matched by gender and age. Differences between groups were investigated using bivariate and multivariate analyses.

Results: The questionnaire response rate in the exposed group was 65.3 % (817/1252) and in the control group 31.4 % (1128/3598). The adjusted odds ratio (OR) for perceived food intolerance for the exposed group was 2.00 with 95 % confidence interval (CI): 1.65 to 2.42, as compared with the control group. Perceived intolerance for dairy products was the most frequently reported intolerance, with an adjusted OR for the exposed of 1.95 (95 % CI: 1.51 to 2.51). Perceived intolerance for fatty foods, vegetables, fruit, cereals and alcohol was also significantly higher in the exposed group. The groups did not differ in perceived intolerance to spicy foods, coffee or soda. The association between exposure to *Giardia* infection and perceived food intolerance differed between the IBS group and the no-IBS group, but IBS was not a significant effect modifier for the association. Perceived intolerance for high FODMAP foods (adjusted OR 1.91) and low FODMAP foods (adjusted OR 1.55) was significantly associated with exposure status.

Conclusion: Exposure to *Giardia* infection was associated with perceived food intolerance 3 years after giardiasis. IBS status did not alter the association between exposure status and perceived food intolerance. Perceived intolerance to high FODMAP foods and low FODMAP foods were both statistically significantly associated with exposure to *Giardia* infection.

Keywords: Irritable bowel syndrome, Food intolerance, FODMAP, *Giardia lamblia*

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Background

Gastroenteritis is a common condition around the globe, both sporadic cases and in larger outbreaks caused by contamination of drinking water or food. Post-infectious irritable bowel syndrome (PI-IBS) as a concept has been known for decades. Studies on patients with enteric infections have shown that 4–31 % develop PI-IBS [1]. Irritable bowel syndrome (IBS) has been described following infections caused by bacteria [1] (*Salmonella, E. coli, Shigella, Campylobacter*), virus [2] (*norovirus*) and parasites [3, 4] (*Giardia lamblia*). The mechanisms underlying the development of the disease are incompletely understood, and treatment options are currently the same as for sporadic irritable bowel syndrome [5].

Irritable bowel syndrome (IBS) is characterized by abdominal pain and/or discomfort related to alterations in bowel habits. It is a highly prevalent condition, and one recent meta-study found the pooled prevalence to be 11.2 % globally, varying according to country and the diagnostic criteria used [6]. It places a heavy burden on both the patient and the society, as measured by quality of life, use of health care resources, and work productivity [7]. The pathophysiologic mechanisms of the disease are yet to be fully understood. Current hypotheses include altered gastrointestinal motility [8], brain-gut-interactions [9] and visceral hypersensitivity [8]. There is a possible role of inflammation, post-infectious low-grade inflammation, genetic and immunologic factors, enteroendocrine cells and altered microbiota, but the results are inconsistent [9]. Patients with IBS often report that certain foods may trigger symptoms, and studies offer some support for this [10, 11]. Perceived food intolerance as a long-term complication after gastrointestinal infections is less investigated.

Effective treatment options for IBS are scarce. A dietary approach that has gained increased interest recently is the low FODMAP-diet. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) are a group of carbohydrates and sugar alcohols that share three functional properties: They are poorly absorbed in the small intestine, they are osmotically active molecules because of their small size, and they are rapidly fermented by bacteria [12]. Because of these characteristics there is a possibility that they may worsen symptoms in IBS patients, particularly in the presence of visceral hypersensitivity. Studies have shown that IBS patients may benefit from a diet low in FODMAP [13–17], but there has been some critique of the methodology in these studies, including the fact that no studies have been conducted on unselected patients from primary care [18]. There is a need for studies that elaborate the role of diet in IBS.

In the autumn of 2004 there was a large outbreak of giardiasis in the city of Bergen on the western coast of Norway. In a controlled follow-up study with nearly 2,000 participants in 2007 it was found that the group subject to *Giardia* infection 3 years prior had a significantly higher prevalence of IBS (46 %) than the control group (14 %) [4].

The aims of the current study were firstly, to compare the prevalence of perceived food intolerance in the two groups; secondly, to explore how this was related to the IBS status in the two groups; and thirdly, to investigate any associations with FODMAP content.

Methods

Participants

During the outbreak of giardiasis in Bergen in 2004, 1252 patients who had infection verified by detection of *Giardia lamblia* in their stools were included and comprised the *Giardia* exposed group. A 2:1 matched control cohort was established by sampling two people of the same age and gender for each exposed patient from the entire population of Bergen. Four controls were excluded due to giardiasis during the outbreak, as self-reported in the study questionnaire. The questionnaires were sent by mail in October 2007, and again one month later to non-respondents. Because of a low response rate in the primary control group, the questionnaire was mailed to an additional 1094 controls in May 2008. Details about the study population have been published previously [4].

Variables

The primary outcome in this report is the respondents' self-reported reactions to food, hereafter referred to as perceived food intolerance in line with previous literature [11, 19]. All respondents were asked the following question (Question A): "Do certain types of food give you abdominal symptoms?" Possible answers were: None, light, moderate and severe. For some analyses, these answers were further dichotomized into none vs. light, moderate or severe. Question A was followed by an open-ended question (Question B): "If you react (to food), to what kind is that?" For respondents who answered "no symptoms" or had a missing answer to Question A but still gave an affirmative response about specific types of food causing symptoms, the response was reclassified as "light". The unmodified "light" category included 582 respondents, whereas the modified one included 606.

The responses to Question B were categorized in accordance with categories used in previous studies on IBS and food intolerance [10, 11, 19, 20], and are hereafter referred to as food categories. A selection of these food categories was further analysed. Reported foods were also categorized based on assumed content of FODMAP (high or low), hereafter referred to as high FODMAP

foods and low FODMAP foods. FODMAP content of the foods reported was assessed using a mobile app developed by a research team at the Department of Gastroenterology, Central Clinical School, Monash University, Melbourne, Victoria, Australia. This reference tool was developed on the basis of results from food quantification studies [21–23]. The coding was also discussed between the first author and the clinical dietician in the research team (GK). A total of 971 respondents answered Question B. Responses that were coded as high FODMAP foods include vegetable, cakes, wheat, milk, apple, pear, prunes, dried fruit, and onions. Examples of responses coded as low FODMAP foods were sugar, cocoa, oil, rice, berries, strawberry, alcohol, soda, and banana. Foods where assumed FODMAP content could not be decided were categorized as "uncertain FODMAP." This category was not further analysed. High FODMAP foods were classified according to what subgroup of FODMAP (oligosaccharides, fructose, polyols or lactose) they might contain. Details concerning the coding of the variables were accounted for in a codebook (available upon request).

Exposure in our study was defined as laboratory confirmed *Giardia lamblia* infection in 2004.

In the current study we wanted to investigate if there was an effect modification by IBS on the association between *Giardia* exposure and perceived food intolerance. IBS was defined according to the Rome III criteria. A detailed description of this part of the questionnaire and the translation procedure has previously been published [4].

Demographic information obtained was age (recorded as a continuous variable, categorized to 20-year groups) gender, marital status (four categories), level of education (three categories), main occupation (originally eight categories, reduced to four in the analyses) and status as a student or not in the autumn of 2004. Mean age was calculated before age was categorized to 20-year groups.

Statistical analyses

Pearson's chi square test (exact) was performed on differences between proportions. Results are reported as percentages with p-values for differences, or as unadjusted and adjusted odds ratios (OR) with 95 % confidence intervals (CI). Confounding and effect modification were evaluated with logistic regression modelling, and in stratified crosstabs with Breslow-Day test. Confounders evaluated were status as student or not in 2004, age, gender, work, income and level of education. All analyses of the primary outcomes were adjusted for gender and age. Effect modification by IBS on the association between exposure and perceived food intolerance was investigated by stratified cross tabulation and Breslow-Day test.

All tests were two-sided. The level of significance was 0.05. The data was analysed using the statistical software SPSS version 22.

Ethical approval

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). Respondents were informed that by completing and submitting the questionnaire, they consented to participate in the study.

Results

The questionnaire response rate was 65.3 % (817/1252) among the *Giardia* exposed and 31.4 % (1128/3598) among controls, giving a total response rate of 40.1 % (1945/4850). Respondents were older than non-respondents (mean age 36.1 vs. 32.9 years, $p < 0.001$). There also were a higher proportion of females among respondents (65.7 % vs. 55.8 %, $p < 0.001$), as previously reported [4, 24]. Out of 1945 participants in total, 1875 (96.4 %) could be classified as having IBS or not. As expected from the matched design, the two groups did not differ with respect to gender and age. Further characteristics of respondents in the exposed and the control group are shown in Table 1.

Question A (if, and to what degree, food was perceived to cause abdominal symptoms) was answered by 95.8 % of the respondents (1864/1945). An additional 19 cases were missing from the combined analyses on IBS status and symptoms (Table 2). Among *Giardia* exposed 63.9 % reported perceived food intolerance as compared to 47.6 % in the control group, giving an adjusted odds ratio of 2.00 (95 % CI: 1.65 to 2.42). When stratifying according to IBS status, there were no significant differences between the exposed and controls in the IBS-group regarding perceived food intolerance. Within the no-IBS group the prevalence of perceived food intolerance was higher among the exposed (49 %) than the controls (42.3 %) (adjusted OR: 1.36, 95 % CI: 1.07 to 1.72). However, the Breslow-Day test for effect modification was negative, meaning that the difference in odds ratio between the IBS and the no-IBS group was not statistically significant.

Question B (types of food perceived to cause symptoms) was answered by 49.9 % (971/1945) (Table 3). Dairy products was the most frequently reported food category, and was reported significantly more often in the exposed group than among controls with an adjusted OR of 1.95 (95 % CI: 1.51 to 2.51). Food categories created based on the responses were (in order of descending frequency given for the total study population in parentheses): Dairy products (292), spicy foods (256),

Table 1 Characteristics of 817 *Giardia* exposed and 1128 controls in Bergen, Norway 3 years after outbreak of *Giardia*-epidemic in 2004

Characteristic	Exposed *N* = 817		Controls *N* = 1128		P
	N	%	N	%	
Age groups, years					0.107
0–19	39	4.8	36	3.2	
20–39	526	64.4	736	65.2	
40–59	187	22.9	276	24.5	
60–79	56	6.9	76	6.7	
80–99	9	1.1	4	0.4	
Females	540	66.1	738	65.4	0.772
Marital Status					0.003
Single	271	33.5	293	26.1	
Married	497	61.4	778	69.3	
Divorced/separated	33	4.1	41	3.7	
Widow/widower	9	1.1	11	1.0	
Education					0.004
Primary school	37	4.7	59	5.3	
Secondary school	169	21.3	308	27.7	
University	587	74.0	746	67.0	
Source of income					<0.001
Working	576	71.1	881	78.7	
Out of Work	70	8.6	96	8.6	
Student	137	16.9	121	10.8	
Other	27	3.3	22	2.0	
Student autumn 2004					<0.001
No	503	62.7	842	75.8	
Yes, full time	261	32.5	229	20.6	
Yes, part time	38	4.7	40	3.6	
IBS	355	46.1	155	14.0	<0.001

Abbreviations: IBS Irritable Bowel Syndrome, *P* P-value from Pearson's chi square (exact)

vegetables (232), cereals (227), milk (163), fruit (120), alcohol (109), meats (93), coffee (91), fatty foods (75), wheat (73), unclassified (46), sweets (45), soda (40), sugar (33), dinners (29), gravy/dressing (28), beer (26), chocolate (25), juice (25), eggs (23), baked goods (22), fish (21), shellfish (21), yeast products (18), smoked food (17), nuts (17), processed food (15), tomato/tomato products (15), fruit juice (14), gluten (11), fibre (8), tea (8), salted food (8), soy (3).

Perceived intolerance to high FODMAP foods was reported more often in the exposed group compared to the control group with an adjusted OR of 1.91 (95 % CI: 1.57 to 2.33), as was intolerance to low FODMAP foods, with an adjusted OR of 1.55 (95 % CI: 1.26 to 1.92). A total of 585 respondents reported intolerance to high FODMAP foods, 461 reported intolerance to low FODMAP foods, and 528 respondents reported intolerance to foods where FODMAP content could not be ascertained. The ORs for high FODMAP foods were somewhat larger than the ORs for low FODMAP foods (Tables 3 and 4). Since these categories were not mutually exclusive, there was no direct way to test the potential differences in strength between these associations statistically.

Perceived food intolerance for specific food categories in the two study groups (*Giardia* group vs. control group) was further analysed according to IBS status. Among respondents with IBS, the *Giardia* group reported vegetables, fruit, alcohol and the FODMAP subgroup polyols significantly more often than did controls. Among respondents without IBS, dairy products, fatty foods, vegetables, fruit, high FODMAP, and the FODMAP subgroups lactose, polyols and fructose were reported significantly more frequently by the *Giardia* exposed group than by controls (Table 4). The test for effect modification by IBS on perceived food intolerance was negative for these data.

We also investigated the difference in perceived food intolerance for the specific food categories between respondents with IBS compared to respondents without IBS when stratified according to exposure status. Within the exposed stratum respondents with IBS had statistically significantly more perceived intolerance for the food categories dairy products, spicy foods, fatty foods, vegetables, fruit, cereals and alcohol. Within the control stratum respondents with IBS had statistically significantly more perceived intolerance for the same food categories as mentioned above except for spicy foods, vegetables and alcohol (Additional file 1: Table S1).

Sub-group analyses on cases with moderate or severe symptoms from intake of food were of low value because of a low number of cases. No association was found between different subtypes of IBS (diarrhoea-predominant, obstipation-predominant, and mixed) and perceived food intolerances (Additional file 2: Table S2).

There was a tendency towards women reporting a higher prevalence of perceived food intolerance for most food categories than men, but this tendency was the same in both the exposed and the control group (Additional file 3: Table S3).

Discussion

The main result of this study is that there was a higher prevalence of perceived food intolerance in the exposed group compared to a control group three years after verified *Giardia* infection. IBS was not an effect modifier for this association. Perceived intolerance to high FODMAP foods and low FODMAP foods were both

Table 2 Perceived food intolerance in *Giardia* exposed ($n = 764$) and a control group ($n = 1100$) 3 years after an outbreak of giardiasis in Bergen, Norway, 2004

Group		Perceived food intolerance[a]														
		No		Yes[b]						Severity of perceived food intolerance						
						Unadjusted		Adjusted[c]		Light		Moderate		Severe		P
	N	n	%	n	%	OR	95 % CI	OR	95 % CI	n	%	n	%	n	%	
Exposure status																
Exposed	764	276	36.1	488	63.9	1.94	1.61 to 2.35	2.00	1.65 to 2.42	238	31.2	168	22.0	82	10.7	<0.001
Control	1100	576	52.4	524	47.6					368	33.5	116	10.5	40	3.6	
IBS status																
IBS	501	98	19.6	403	80.4	5.16	4.04 to 6.60	5.03	3.93 to 6.45	147	29.3	167	33.3	89	17.8	<0.001
No-IBS	1344	748	55.7	596	44.3					451	33.6	113	8.4	32	2.4	
Within IBS																
Exposed	348	65	18.7	283	81.3	1.20[d]	0.75 to 1.92	1.25	0.78 to 2.01	105	30.2	111	31.9	67	19.3	0.418
Control	153	33	21.6	120	78.4					42	27.5	56	36.6	22	14.4	
Within No-IBS																
Exposed	406	207	51.0	199	49.0	1.31[d]	1.04 to 1.66	1.36	1.07 to 1.72	130	32.0	55	13.5	14	3.4	<0.001
Control	938	541	57.7	397	42.3					321	34.2	58	6.2	18	1.9	

Abbreviations: IBS irritable bowel syndrome, *P* p-value from Pearson's chi square test (exact), *CI* confidence interval, *OR* odds ratio
[a]The question pertaining to these categories was: "Do certain types of food give you abdominal symptoms?" with four alternatives: none, light, moderate, severe
[b]Four level response variable dichotomized to no (none) vs. yes (light, moderate or severe)
[c]Adjusted for gender and age
[d]The Breslis reasonably high, howeverow-Day test was non-significant

statistically significantly associated with exposure to *Giardia* infection.

Limitations and strengths

Some of the limitations regarding the data used in this study have been described before [4, 24]. The response rate in the exposed group (65,3 %) is reasonably high, however, selection bias cannot be ruled out. This may impact the prevalence, but estimates of association are more robust. The exposed group is selected on the basis of having seen a doctor and thus having had giardiasis diagnosed by positive stool samples. The differences in characteristics of this group compared to those who might have had giardiasis without seeking medical attention is not known. Unbiased baseline information about IBS, food intolerance, previous gastrointestinal infections or other illnesses is impossible to obtain, as this may be regarded as a natural, unplanned experiment. However, this problem of missing information is similar for the exposed group and the control group, and most of these factors are presumed to be equally distributed between the two groups prior to the giardiasis outbreak.

The exposed group has had a defined gastrointestinal illness that may lead to increased wariness of possible causes of their abdominal complaints, including food intolerance. Hence they might not actually be more susceptible to intolerance per se.

The response rate in the control group (31.4 %) is relatively low and there is a risk of selection bias. The prevalence of IBS in our control group is 14.0 %, which is a little higher than 8.4 %, the prevalence in the general Norwegian population as found in a large public health survey in 2006 [25]. Our study used the Rome III criteria, which have been shown in a study [26] to find a higher prevalence of IBS than the Rome II criteria used in the above-mentioned study. In sum, this may indicate that our control group is not too dissimilar from the general population. Again, the investigation of associations, with use of relative outcome measures such as OR, depends to a lesser degree on such biases.

The questionnaire items about food have not been validated, and the reliability is not known. They do not constitute a complete assessment of the respondents' diet. The classification of an open-ended question may be subject to interpreter bias, and there is a potential for misclassification to a varying degree depending on the specific category. All food categories and how the answers were coded were accounted for in a codebook. Although quantitative analyses on qualitative data is not straight forward, one advantage of using an open-ended question instead of a closed-ended one is that it is unguided by any preconceived theory. The respondents were free to answer whichever type of food they perceived as giving symptoms. Also, there were 971 responses to the open-ended question, many of which were readily and unambiguously coded to meaningful food categories. This study was performed in 2007, before the concept of FODMAP-content in the diet was generally known, and the responses will

Table 3 Perceived food intolerance according to food categories and FODMAP content in 817 *Giardia* exposed and 1128 controls three years after an outbreak of giardiasis in Bergen, Norway, 2004

	Exposed $N = 817$		Controls $N = 1128$		Unadjusted		Adjusted[b]	
Food categories[a]	n	%	n	%	OR[c]	95 % CI	OR[c]	95 % CI
Food categories								
Dairy products	163	20.0	129	11.4	**1.93**	**1.50 to 2.48**	**1.95**	**1.51 to 2.51**
Spicy foods	119	14.6	137	12.1	1.23	0.95 to 1.61	1.25	0.96 to 1.63
Fatty foods	48	5.9	27	2.4	**2.55**	**1.57 to 4.12**	**2.63**	**1.62 to 4.26**
Vegetables	118	14.4	114	10.1	**1.50**	**1.14 to 1.98**	**1.56**	**1.18 to 2.06**
Fruit	75	9.2	45	4.0	**2.43**	**1.66 to 3.56**	**2.45**	**1.67 to 3.60**
Cereals	128	15.7	99	8.8	**1.93**	**1.46 to 2.55**	**1.98**	**1.49 to 2.62**
Alcohol	66	8.1	43	3.8	**2.22**	**1.49 to 3.29**	**2.29**	**1.54 to 3.40**
Coffee	39	4.8	52	4.6	1.04	0.68 to 1.59	1.05	0.68 to 1.61
Soda	17	2.1	23	2.0	1.02	0.54 to 1.92	1.03	0.55 to 1.94
FODMAP Content[d]								
High FODMAP	308	37.7	277	24.6	**1.86**	**1.53 to 2.26**	**1.91**	**1.57 to 2.33**
Low FODMAP	230	28.2	231	20.5	**1.52**	**1.23 to 1.88**	**1.55**	**1.26 to 1.92**
FODMAP subtype								
Oligosaccharides	190	23.3	187	16.6	**1.53**	**1.22 to 1.91**	**1.58**	**1.25 to 1.99**
Lactose	156	19.1	128	11.3	**1.84**	**1.43 to 2.38**	**1.86**	**1.44 to 2.40**
Polyols	78	9.5	45	4.0	**2.54**	**1.74 to 3.71**	**2.57**	**1.76 to 3.77**
Fructose	71	8.7	39	3.5	**2.66**	**1.78 to 3.97**	**2.69**	**1.80 to 4.02**

Abbreviations: FODMAP fermentable oligo-, di- and monosaccharides and polyols; *IBS* irritable bowel syndrome; *CI* confidence interval; *OR* Odds ratio.
[a]The question pertaining to these categories was: "If you react (to food), to what kind is that?"
[b]Adjusted for gender and age
[c]Statistically significant ORs are presented in **bold** font
[d]Assumed FODMAP content of the response(s) to the open-ended question about food

not be biased by the recent interest in this diet. Based on these considerations we found that a quantitative approach was justified.

Interpretation

Perceived food intolerance in a post-infectious setting has been scarcely investigated. Short-term lactose malabsorption after giardiasis has been described, but with contradictory findings [27, 28]. Fat malabsorption with steatorrhoea and diarrhoea can occur in chronic giardiasis, as can folate, B12 and vitamin A deficiency [27], but these are usually resolved with appropriate treatment. In our study the prevalence of perceived intolerance for both dairy products and fatty foods is relatively high, and significantly higher in the exposed than in the control group. Our study is not designed to investigate the mechanisms behind perceived food intolerance.

Recent studies and reviews have elucidated some of the mechanisms behind the development of PI-IBS after infective gastroenteritis [1]. Similar pathophysiologic mechanisms have also been found in sporadic IBS [9]. In this study we find a similar pattern of perceived food intolerance among *Giardia* exposed respondents with IBS (predominantly PI-IBS) and controls with IBS (sporadic IBS), but with a tendency, sometimes statistically significant, towards the exposed more often reporting intolerance for the specific food categories. Our results do not help clarify whether PI-IBS might be the same entity as sporadic IBS.

The prevalence of IBS and perceived food intolerance were measured at the same time. No inferences about causative pathways between IBS and perceived food intolerance can be made. We found that the exposed had a higher prevalence of perceived food intolerance than controls, and it has previously been found that this group has a higher prevalence of IBS [4]. There was also a significantly higher prevalence of perceived food intolerance among exposed in the no-IBS group. One hypothesis is that giardiasis causes alterations in the gastrointestinal tract that are important in the pathogenesis of both IBS and food intolerance. This does not suggest that the pathogenesis is identical, but there might be some common immunological pathways involved.

In our study 81.3 % of respondents with IBS in the exposed group and 78.4 % with IBS in the control group reported perceived food intolerance when this was defined as light, moderate or severe food-related abdominal complaints. Among respondents without IBS the

Table 4 Comparison of 770 *Giardia* exposed and 1105 controls stratified to IBS status, on perceived food intolerance according to food categories and FODMAP content 3 years after outbreak of a Giardia-epidemic in Bergen, Norway, 2004

	IBS N = 510								No-IBS N = 1365							
	Exposed *N* = 355		Controls *N* = 155		Unadjusted		Adjusted[b]		Exposed *N* = 415		Controls *N* = 950		Unadjusted		Adjusted[b]	
Food categories[a]	n	%	n	%	OR	95% CI	OR	95 % CI	n	%	n	%	OR	95 % CI	OR	95 % CI
Food Categories																
Dairy products	96	27.0	38	24.5	1.14	0.74 to 1.76	1.18	0.76 to 1.84	64	15.4	90	9.5	1.74	1.24 to 2.46	1.78	1.26 to 2.53
Spicy foods	69	19.4	26	16.8	1.20	0.73 to 1.97	1.24	0.75 to 2.04	48	11.6	109	11.5	1.01	0.70 to 1.45	1.04	0.72 to 1.49
Fatty foods	31	8.7	8	5.2	1.76	0.79 to 3.92	1.79	0.80 to 4.02	16	3.9	18	1.9	2.08	1.05 to 4.11	2.19	1.10 to 4.34
Vegetables	79	22.3	24	15.5	1.56	0.95 to 2.58	1.69	1.02 to 2.81	39	9.4	89	9.4	1.00	0.68 to 1.49	1.08	0.72 to 1.60
Fruit	49	13.8	12	7.7	1.91	0.99 to 3.70	2.04	1.05 to 3.97	25	6.0	31	3.3	1.90	1.11 to 3.26	1.96	1.14 to 3.38
Cereals	91	25.6	36	23.2	1.14	0.73 to 1.77	1.21	0.77 to 1.89	36	8.7	63	6.6	1.34	0.87 to 2.05	1.41	0.91 to 2.16
Alcohol	43	12.1	8	5.2	2.53	1.16 to 5.52	2.57	1.18 to 5.61	22	5.3	34	3.6	1.51	0.87 to 2.61	1.55	0.89 to 2.69
Coffee	23	6.5	12	7.7	0.83	0.40 to 1.70	0.84	0.40 to 1.73	16	3.9	40	4.2	0.91	0.51 to 1.65	0.92	0.51 to 1.66
Soda	9	2.5	6	3.9	0.65	0.23 to 1.85	0.67	0.23 to 1.91	7	1.7	17	1.8	0.94	0.39 to 2.29	0.96	0.39 to 2.34
FODMAP Content[c]																
High FODMAP	186	52.4	74	47.7	1.21	0.83 to 1.76	1.27	0.87 to 1.87	116	28.0	201	21.2	1.45	1.11 to 1.88	1.51	1.15 to 1.98
Low FODMAP	145	40.8	57	36.8	1.19	0.81 to 1.75	1.22	0.83 to 1.80	83	20.0	171	18.0	1.14	0.85 to 1.53	1.17	0.88 to 1.58
FODMAP subtype																
Oligosaccharides	131	36.9	51	32.9	1.19	0.80 to 1.78	1.29	0.86 to 1.94	58	14.0	135	14.2	0.98	0.70 to 1.37	1.04	0.74 to 1.46
Lactose	93	26.2	39	25.2	1.06	0.69 to 1.63	1.09	0.70 to 1.69	60	14.5	88	9.3	1.66	1.17 to 2.35	1.69	1.19 to 2.41
Polyols	51	14.4	13	8.4	1.83	0.97 to 3.48	1.91	1.01 to 3.65	25	6.0	31	3.3	1.90	1.11 to 3.26	1.95	1.14 to 3.36
Fructose	45	12.7	14	9.0	1.46	0.78 to 2.75	1.49	0.79 to 2.81	24	5.8	25	2.6	2.27	1.28 to 4.03	2.31	1.30 to 4.11

Abbreviations: FODMAP fermentable oligo-, di- and monosaccharides and polyols; *IBS* irritable bowel syndrome; *CI* confidence Interval; *OR* Odds ratio
[a]The question pertaining to these categories was: "If you react (to food), to what kind is that?"
[b]Adjusted for gender and age
[c]Assumed FODMAP content of the response(s) to the open-ended question about food

proportions were 49.0 and 42.3 %, respectively. These results were comparable to a recent dietary survey performed on Irish IBS-patients (89.6 %) and a comparative group (55.0 %) [29]. The results for the non-IBS group is higher than what was found in a general UK population in 1994 (20.4 %) [30]. Other studies on IBS and perceived food intolerances have found prevalence ranging from 25 to 70 % [11, 19, 31, 32]. The reasons for the variance in prevalence of perceived food intolerance reported between studies might be due to different ways of measuring food intolerance, because of differences in the IBS-populations under investigation (e.g. inpatient vs. outpatient), and maybe due to a development in dietary trends over time.

Milk, dairy products, wheat products, caffeine, certain meat, certain vegetables, hot spices, alcohol, fat, fibre, fried food and smoked products are some of the foods stated in other studies to cause symptoms in IBS patients [10, 20]. The first nine of these food categories are also among the quantitatively most important in all investigated groups in our study, whereas the latter three are less frequently reported. Some of the above-mentioned food categories (dairy products, fatty foods and cereals) are significantly associated with IBS both in the exposed group and the control group. There are some similarities between the findings in our study and other studies on IBS and diet [10, 20]. However, as the validity and reliability of our questionnaire-items regarding food have not been tested, the results must be interpreted with caution.

There is a general tendency that the prevalence of perceived food intolerance for the various foods in our study is lower than that in other studies [11, 19, 29]. This could be due to the fact that most of the other studies use questionnaires with a predefined checklist of food items, which is known to overestimate the prevalence of intolerance to the included food items [33]. However, the prevalence of perceived food intolerance in our study is also lower than those reported in another study that used an open-ended question to map food perceived to cause symptoms [29]. This could be partially explained by a stricter coding of some of the food categories in our study, and also due to the fact that the patients included in the study were recruited from a gastroenterology clinic, and might thus be more severely ill than our respondents, who were recruited from the general population.

We found a statistically significant association between exposure status and perceived intolerance to both high and low FODMAP foods. Because the categories of high and low FODMAP foods were not mutually exclusive, the strength of the associations could not be compared statistically, but rather the results had to be interpreted more subjectively. The OR for high FODMAP foods was slightly higher than that for low FODMAP foods both in the unstratified and stratified (according to IBS-status) analyses, but with substantial overlap of the confidence intervals (Tables 3 and 4). The current study does not contradict or support the findings from other studies suggesting that high FODMAP content may add to symptoms among vulnerable individuals.

Food intolerance in IBS should be further investigated, especially with randomized controlled diet intervention studies in primary health care. We would propose that such a diet could be based on the FODMAP concept, but also include a tailor-made diet based on the patient's perceived intolerances, followed by reintroduction.

Conclusion

Giardia exposed participants had a higher prevalence of perceived food intolerance than a control group three years after acute gastroenteritis. The association between exposure to *Giardia* infection and perceived food intolerance differed between the IBS group and the no-IBS group, but IBS was not a significant effect modifier for the association. There was a significantly higher prevalence of perceived intolerance to foods both high and low in FODMAP content in the exposed group as compared to the control group. Our findings did not indicate a stronger association between *Giardia* exposure and perceived intolerance to high FODMAP foods as compared to low FODMAP foods.

Additional files

Additional file 1: Table S1. Comparison of perceived food intolerance according to food categories and FODMAP content among Giardia exposed and a control group, stratified according to IBS status. 3 years after outbreak of giardiasis in Bergen, Norway, 2004. (DOCX 33 kb)

Additional file 2: Table S2. Perceived food intolerance according to IBS subtype among Giardia exposed ($n = 355$) and controls ($n = 155$) with IBS 3 years after an outbreak of giardiasis in Bergen, Norway, 2004. (DOCX 36 kb)

Additional file 3: Table S3. Comparison of 817 Giardia exposed and 1128 controls stratified according to gender, on perceived food intolerance in general and according to food categories and FODMAP content 3 years after outbreak of a Giardia-epidemic in Bergen, Norway, 2004. (DOCX 24 kb)

Competing interests

KH has served on an Advisory board for Lupin Pharmaceuticals, Baltimore, SA. He has no other competing interests. All other authors declare that they have no competing interests.

Authors' contributions

SL is the main author. He has performed the analyses. He has done the main writing of the article, and worked with interpretation of the results. KAW contributed to the design, interpretation of the results, and writing. GEE contributed to the analyses, interpretation of the results, and writing. KH contributed to the design, the writing and the interpretation of the results. GK contributed to the coding of the outcome variables and interpretation of the results. NL contributed to the design, the writing and the interpretation of the results. GR contributed to the design, analyses, writing and interpretation of the results. All authors have revised the article for intellectual content, and approved the final version to be published.

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Table S1: Comparison of perceived food intolerance according to food categories and FODMAP content among *Giardia* exposed and a control group, stratified according to IBS status. 3 years after outbreak of giardiasis in Bergen, Norway, 2004.

	Exposed N=770								Controls N=1105							
	IBS N=355		No-IBS N=415		Unadjusted		Adjusted[b]		IBS N=155		No-IBS N=950		Unadjusted		Adjusted[b]	
Food categories[a]	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**OR**	**95% CI**
Food Categories																
Dairy products	96	27.0	64	15.4	2.03	1.43 to 2.90	1.96	1.37 to 2.81	38	24.5	90	9.5	3.10	2.03 to 4.75	2.96	1.92 to 4.54
Spicy foods	69	19.4	48	11.6	1.85	1.24 to 2.75	1.77	1.18 to 2.65	26	16.8	109	11.5	1.56	0.98 to 2.48	1.48	0.93 to 2.37
Fatty foods	31	8.7	16	3.9	2.39	1.28 to 4.44	2.27	1.21 to 4.23	8	5.2	18	1.9	2.82	1.20 to 6.60	2.76	1.17 to 6.49
Vegetables	79	22.3	39	9.4	2.76	1.82 to 4.17	2.54	1.67 to 3.86	24	15.5	89	9.4	1.77	1.09 to 2.88	1.61	0.99 to 2.64
Fruit	49	13.8	25	6.0	2.50	1.51 to 4.14	2.37	1.42 to 3.95	12	7.7	31	3.3	2.49	1.25 to 4.96	2.28	1.14 to 4.57
Cereals	91	25.6	36	8.7	3.63	2.39 to 5.51	3.41	2.24 to 5.20	36	23.2	63	6.6	4.26	2.71 to 6.69	3.98	2.52 to 6.28
Alcohol	43	12.1	22	5.3	2.46	1.44 to 4.20	2.43	1.42 to 4.15	8	5.2	34	3.6	1.47	0.67 to 3.23	1.46	0.66 to 3.23
Coffee	23	6.5	16	3.9	1.73	0.90 to 3.32	1.73	0.90 to 3.35	12	7.7	40	4.2	1.91	0.98 to 3.73	1.90	0.97 to 3.72
Soda	9	2.5	7	1.7	1.52	0.56 to 4.11	1.46	0.54 to 3.98	6	3.9	17	1.8	2.21	0.86 to 5.70	2.11	0.82 to 5.45
FODMAP Content[c]																
High FODMAP	186	52.4	116	28.0	2.84	2.10 to 3.83	2.72	2.01 to 3.69	74	47.7	201	21.2	3.40	2.40 to 4.84	3.24	2.27 to 4.62
Low FODMAP	145	40.8	83	20.0	2.76	2.01 to 3.81	2.66	1.92 to 3.67	57	36.8	171	18.0	2.65	1.84 to 3.82	2.56	1.77 to 3.69
FODMAP subtype																
Oligosaccharides	131	36.9	58	14.0	3.60	2.53 to 5.12	3.39	2.37 to 4.85	51	32.9	135	14.2	2.96	2.02 to 4.34	2.73	1.85 to 4.03
Lactose	93	26.2	60	14.5	2.10	1.46 to 3.02	2.03	1.41 to 2.94	39	25.2	88	9.3	3.29	2.16 to 5.03	3.15	2.05 to 4.84
Polyols	51	14.4	25	6.0	2.62	1.59 to 4.32	2.50	1.51 to 4.14	13	8.4	31	3.3	2.71	1.39 to 5.31	2.55	1.30 to 5.00
Fructose	45	12.7	24	5.8	2.37	1.41 to 3.97	2.30	1.37 to 3.88	14	9.0	25	2.6	3.67	1.87 to 7.24	3.57	1.81 to 7.05

Abbreviations: FODMAP: fermentable oligo-, di- and monosaccharides and polyols; IBS: irritable bowel syndrome; CI: confidence Interval; OR: Odds ratio.

a The question pertaining to these categories was: "If you react (to food), to what kind is that?"

b Adjusted for gender and age.

c Assumed FODMAP content of the response(s) to an open-ended question about food.

Table S2: Perceived food intolerance according to IBS subtype among *Giardia* exposed (n = 355) and controls (n = 155) with IBS three years after an outbreak of giardiasis in Bergen, Norway, 2004

	Perceived food intolerance[a,b]									
	Overall[a]		**Food category[b]**							
	Yes[a]		**Dairy products**		**Spicy foods**		**High FODMAP**		**Low FODMAP**	
Group	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
IBS Constipation	51	81.0	14	21.5	7	10.8	33	50.8	21	32.3
IBS Diarrhoea	150	81.1	47	24.9	37	19.6	96	50.8	79	41.8
IBS Mixed	171	81.4	60	28.2	47	22.1	111	52.1	88	41.3
IBS Unsubtyped	31	72.1	13	30.2	4	9.3	20	46.5	14	32.6
P-value		0.553		0.640		0.076		0.928		0.395

Abbreviations: FODMAP: fermentable oligo-, di- and monosaccharides and polyols; IBS: irritable bowel syndrome; P-value: p-value from Pearson's chi square test (2-sided).

a The question pertaining to this category was: "Do certain types of food give you abdominal symptoms?" with four alternatives: none, light, moderate, severe, dichotomized to no (none) vs. yes (light, moderate or severe)

b The question pertaining to these categories was: "If you react (to food), to what kind is that?"

Table S3: Comparison of 817 *Giardia* exposed and 1128 controls stratified according to gender, on perceived food intolerance in general and according to food categories and FODMAP content 3 years after outbreak of a Giardia-epidemic in Bergen, Norway, 2004.

	Females N=1278						Males N=667					
Perceived food intolerance	**Exposed N=540**		**Controls N=738**		**Unadjusted**		**Exposed N=277**		**Controls N=390**		**Unadjusted**	
	n	**%**	**n**	**%**	**OR[e]**	**95% CI**	**n**	**%**	**n**	**%**	**OR[e]**	**95% CI**
Overall[a]												
Yes[b]	347	69.1	372	51.5	2.11	1.66 to 2.68	141	53.8	152	40.2	1.73	1.26 to 2.38
Food Categories[c]												
Dairy products	127	23.5	104	14.1	1.88	1.41 to 2.50	36	13.0	25	6.4	2.18	1.28 to 3.73
Spicy foods	89	16.5	96	13.0	1.32	0.97 to 1.80	30	10.8	41	10.5	1.03	0.63 to 1.70
FODMAP Content[c,d]												
High FODMAP	232	43.0	218	29.5	1.80	1.42 to 2.27	76	27.4	59	15.1	2.12	1.45 to 3.11
Low FODMAP	166	30.7	158	21.4	1.63	1.26 to 2.10	64	23.1	73	18.7	1.31	0.89 to 1.90

Abbreviations: FODMAP: fermentable oligo-, di- and monosaccharides and polyols; IBS: irritable bowel syndrome; CI: confidence Interval; OR: Odds ratio.

a N=1224 for females (Exposed N=502, controls N=722) and N=640 for males (Exposed N=262, controls N=378) for this category.

b The question pertaining to this category was: "Do certain types of food give you abdominal symptoms?" with four alternatives: none, light, moderate, severe, dichotomized to no (none) vs. yes (light, moderate or severe)

c The question pertaining to these categories was: "If you react (to food), to what kind is that?"

d Assumed FODMAP content of the response(s) to an open-ended question about food.

e Breslow-Day test of homogeneity of the odds ratios between the two genders was negative for each category.

PAPER 2

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Prevalence of Irritable Bowel Syndrome and Chronic Fatigue 10 Years After *Giardia* Infection

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BACKGROUND & AIMS: **Irritable bowel syndrome (IBS) is a complication that can follow gastrointestinal infection, but it is not clear if patients also develop chronic fatigue. We investigated the prevalence and odds ratio of IBS and chronic fatigue 10 years after an outbreak of *Giardia lamblia*, compared with a control cohort, and changes in prevalence over time.**

METHODS: **We performed a prospective follow-up study of 1252 laboratory-confirmed cases of giardiasis (exposed), which developed in Bergen, Norway in 2004. Statistics Norway provided us with information from 2504 unexposed individuals from Bergen, matched by age and sex (controls). Questionnaires were mailed to participants 3, 6, and 10 years after the outbreak. Results from the 3- and 6-year follow-up analyses have been published previously. We report the 10-year data and changes in prevalence among time points, determined by logistic regression using generalized estimating equations.**

RESULTS: **The prevalence of IBS 10 years after the outbreak was 43% (n = 248) among 576 exposed individuals and 14% (n = 94) among 685 controls (adjusted odds ratio for development of IBS in exposed individuals, 4.74; 95% CI, 3.61–6.23). At this time point, the prevalence of chronic fatigue was 26% (n = 153) among 587 exposed individuals and 11% (n = 73) among 692 controls (adjusted odds ratio, 3.01; 95% CI, 2.22–4.08). The prevalence of IBS among exposed persons did not change significantly from 6 years after infection (40%) to 10 years after infection (43%; adjusted odds ratio for the change 1.03; 95% CI, 0.87–1.22). However, the prevalence of chronic fatigue decreased from 31% at 6 years after infection to 26% at 10 years after infection (adjusted odds ratio for the change 0.74; 95% CI, 0.61–0.90).**

CONCLUSION: **The prevalence of IBS did not change significantly from 6 years after an outbreak of *Giardia lamblia* infection in Norway to 10 years after. However, the prevalence of chronic fatigue decreased significantly from 6 to 10 years afterward. IBS and chronic fatigue were still associated with giardiasis 10 years after the outbreak.**

Keywords: Epidemiology; Bacteria; Microbiota; Long-Term Outcome.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that constitutes a substantial economic burden to society.[1] It is a common condition, with a pooled prevalence of 11.2%.[1] Chronic fatigue (CF) is another common complaint among patients seeking primary care, and 1 study found a prevalence of 24% in this population.[2] Despite its potentially debilitating features, it is less investigated. Fatigue is more commonly studied as part of the less prevalent CF syndrome (CFS).[3] IBS and CF or CFS share a lack of consistent biologic findings and both conditions are often categorized as functional disorders.[4]

Etiology for both IBS and CF is incompletely understood, but both conditions have been associated with previous infections.[3,5] Postinfectious IBS (PI-IBS) has been described following outbreaks, among travelers returning from abroad, or as sporadic cases.[5–10] The rate of recovery from PI-IBS varies between studies, and

Abbreviations used in this paper: **AFE, attributable fraction among the exposed; aOR, adjusted odds ratio; CF, chronic fatigue; CFS, chronic fatigue syndrome; CI, confidence interval; IBS, irritable bowel syndrome; OR, odds ratio; PI-IBS, post-infectious irritable bowel syndrome.**

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bacterial infections seem to be associated with more prolonged symptoms than viral infections.[10] One study after an outbreak of bacterial dysentery reported that IBS was associated with exposure up to 8 years after the acute infection.[6] A more recent study found that IBS was associated with shigellosis after 1 and 3 years' postexposure follow-up, but not after 5, 8, or 10 years.[7] Postinfectious CF as part of CFS has been reported as a complication after various acute viral and bacterial infections.[3,11–14]

In the autumn of 2004, the parasite *Giardia lamblia* contaminated 1 of the municipal drinking-water reservoirs in Bergen, likely due to broken sewage pipes. This is one of the largest waterborne outbreaks ever recorded in Norway,[15] and 1252 patients had laboratory confirmed giardiasis that was linked to the outbreak.[9] Several postinfectious conditions have been studied in this cohort over time, and our research group has previously found an association between *Giardia lamblia* infection and IBS and CF both 3 and 6 years after the acute illness.[8,9] The prevalence fell from 3 to 6 years for both conditions.

The primary aim of the current study was to estimate the prevalence and odds ratio of IBS and CF 10 years after acute giardiasis relative to a control cohort. The secondary aims were to investigate changes in prevalence from 3 to 10 and from 6 to 10 years and to estimate incidence, recovery, and persistence of these conditions.

Methods

Participants

This study was a prospective follow-up of a cohort of 1252 patients (the exposed group) and a control group 3, 6, and 10 years after laboratory verified *Giardia* infection during a waterborne outbreak in the autumn of 2004. On our request, Statistics Norway established a 2:1 control group of 2504 individuals from Bergen matched by age and sex. There was a predominance of women in the exposed target population (61%, 764 of 1252). Children under 18 years of age were excluded from the data collection at the 10-year follow-up, and hence these children were retrospectively also excluded from all analyses based on the data collections at the 3- and 6-year follow-ups (Table 1). Analyses of prevalence changes from 3 to 6 years[8] have been published previously, but were calculated anew for this study. The Regional Committee for Ethics in Medical Research approved the study (ref. no. 2014/1372).

Variables

The primary outcome variables were IBS and CF 10 years after giardiasis in the exposed and the control group, as well as the following subgroup categories: severe IBS, severe CF, IBS, and CF combined, IBS only and CF only. Secondary outcomes were changes in prevalence of IBS and CF from 3 to 10 years (for IBS and CF only), and from 6 to 10 years (all subgroup categories). Respondents who had either IBS or CF at all 3 follow-ups were defined as having a persistent condition.

IBS was defined according to the Rome III criteria,[16] where respondents who had recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months were defined as having IBS if their pain or discomfort was also associated with 2 or more of the additional IBS criteria. These symptoms must also have had an onset at

Table 1. Cohorts Available for Analyses 3, 6, and 10 Years After a *Giardia lamblia* Outbreak in Bergen, Norway, 2004

	Exposed[a]		Control subjects[b]		Total	
Cohort	n	%	n	%	n	%
Original target population 2007	1252	100	2504	100	3756	100
Children removed[c]	34		68		102	
Target population 2007	1218	100	2436	100	3654	100
Study population 2007	802	66	843	35	1645	45
Lost to follow-up[d]	13		58			
Target population 2010	1205	100	2378	100	3583	100
Study population 2010	731	61	852	36	1583	44
Lost to follow-up[d]	29		48			
Target population 2015	1176	100	2330	100	3506	100
Questionnaires returned 2015	592	50	709	30	1301	37
Giardia during outbreak			6			
Incomplete response	2		6			
Withdrawn questionnaire			1			
Nonresponders	584		1622		2206	
Study population 2015	590	50	696	30	1286	37
Responded at all follow-ups	427	36	365	16	792	23

[a] *Giardia* exposed in 2004.
[b] Sex and age matched controls from Bergen, Norway.
[c] Children younger than 18 years of age in 2015 were removed from original (and subsequent) target populations.
[d] Emigrated, died, withdrawn, or address not found.

least 6 months before the response. When IBS limited daily activities at least often, we defined this as severe IBS. We also defined the IBS subtypes according to the Rome III criteria.[16]

Fatigue was defined using the validated Fatigue Questionnaire.[17] The questionnaire consists of 13 questions, with 11 questions addressing different aspects of fatigue. The severity of fatigue was reported on a 4 item Likert-type scale with responses ranging from 0 (less than normal) to 3 (much more than normal). The scores were added for a total fatigue score (range, 0–33). The scores were also dichotomized (0 and 1 into 0, 2, and 3 into 1) and CF was defined as a dichotomized score of 4 or more, provided the symptoms had lasted 6 months or more. Severe fatigue was defined as CF with a total fatigue score of 23 or more. Cases with more than 4 missing answers on the 11 fatigue related questions were excluded from the analyses on CF. In cases with 4 or less missing responses the missing values were replaced with the mean of all the responses to that particular question.

Demographic variables recorded and evaluated as potential confounders were sex, age, marital status, educational level, and main occupation. Sex and age were additionally considered as potential interacting variables for the associations between the exposure and the outcomes.

Nonresponders were compared with responders on age and sex, and only included in nonresponder analyses.

Analyses and Statistical Methods

Descriptive statistics were calculated as percentage or mean. Fisher's exact 2-sided mid-*P* test in 2 × 2 tables was used for binary outcomes,[18] and Pearson's chi square exact 2-sided test for associations in 2 × k tables was used for multilevel outcomes. Gosset's unpaired *t* test was used to compare means for continuous variables.[19]

Selection bias analyses were performed and details regarding these are available as supplementary text.

Prevalence at 10 years was compared between the *Giardia* exposed and controls using odds ratio (OR) with 95% confidence interval (CI). Binary logistic regression and cross-tabulations were used when analyzing CF and IBS to assess risk factors. Interactions were tested by the Breslow-Day test for homogeneity of odds ratios after stratification.

The attributable fraction among the exposed (AFE) was calculated as a percentage by the formula AFE % = (1 – 1/RR) × 100%.

Changes in prevalence between follow-ups were calculated using binary logistic regression with the method of generalized estimating equations. This method accounts for correlation between repeated measures and the matched design. Data from all the respondents from all time points were included. The results from these analyses were presented as age- and sex-adjusted OR (aOR).

Frequencies of incident, recovered and persistent IBS or CF were calculated in 2 × k tables. Associations between exposure and persisting IBS or CF were evaluated by binary logistic regression with calculations of age and sex aOR.

All tests were 2 sided with a level of statistical significance set to .05. All analyses were done using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY). Sankey diagrams used for Figure 1 and Supplementary Table 3 with figure were plotted using R[20] with the package sankeyD3.[21]

Results

The response rate at the 10-year follow-up was 50% (592 of 1176) among the exposed, and 30% (708 of 2330) among control subjects (Table 1). Responders to the 10-year questionnaire were older (43.3 years) than nonresponders (41.0 years, $P < .001$). There were more women among responders (857 of 1300, 66%) than among nonresponders (1307 of 2206, 59%; $P < .001$). Demographically, the exposed and the control group differed only in marital status after 10 years (Table 2).

Results from selection bias analyses are available as supplementary text and Supplementary Tables 1 and 2.

The prevalence of IBS 10 years after the outbreak was 43% (248 of 576) in the exposed group and 14% (94 of 685) in the control group, giving an aOR for IBS among the *Giardia* exposed of 4.74 (95% CI, 3.61–6.23). The AFE for IBS was among *Giardia* exposed was 68% (95% CI, 61%–74%).

The prevalence of CF was 26% (153 of 587) among exposed and 11% (73 of 692) among controls, with an aOR of 3.01 (95% CI, 2.22–4.08). The AFE for CF was 60% (95% CI, 48%–69%). Corresponding figures for the subgroup outcomes are presented in Table 3.

The prevalence of IBS was 44% (169 of 388) among women in the exposed group and 42% (79 of 188) among men ($P = .79$). The prevalence of IBS among women in the control group was 16% (71 of 446) and among men it was 10% (23 of 239, $P = .03$). The Breslow-Day test for interaction between exposure and sex was negative ($P = .10$). Sex was not a risk factor for CF in any of the groups. Age was not a risk factor for any of the conditions in either of the groups.

The decrease in prevalence of IBS in the exposed cohort from 3 (47%) to 6 (40%) years (as previously reported[8]) had an aOR for the change of 0.73 (95% CI, 0.62–0.86). The decrease in prevalence of IBS from 3 (47%) to 10 (43%) years in this cohort had an aOR for the change of 0.75 (95% CI, 0.63–0.90). No change was found from 6 to 10 years. In the control group, there were no changes in prevalence of IBS for any time period (Table 4).

The prevalence of CF in the exposed cohort decreased from 3 (47%) to 6 (31%) years[8] after exposure with an aOR for the change of 0.53 (95% CI, 0.46–0.62), from 3 to

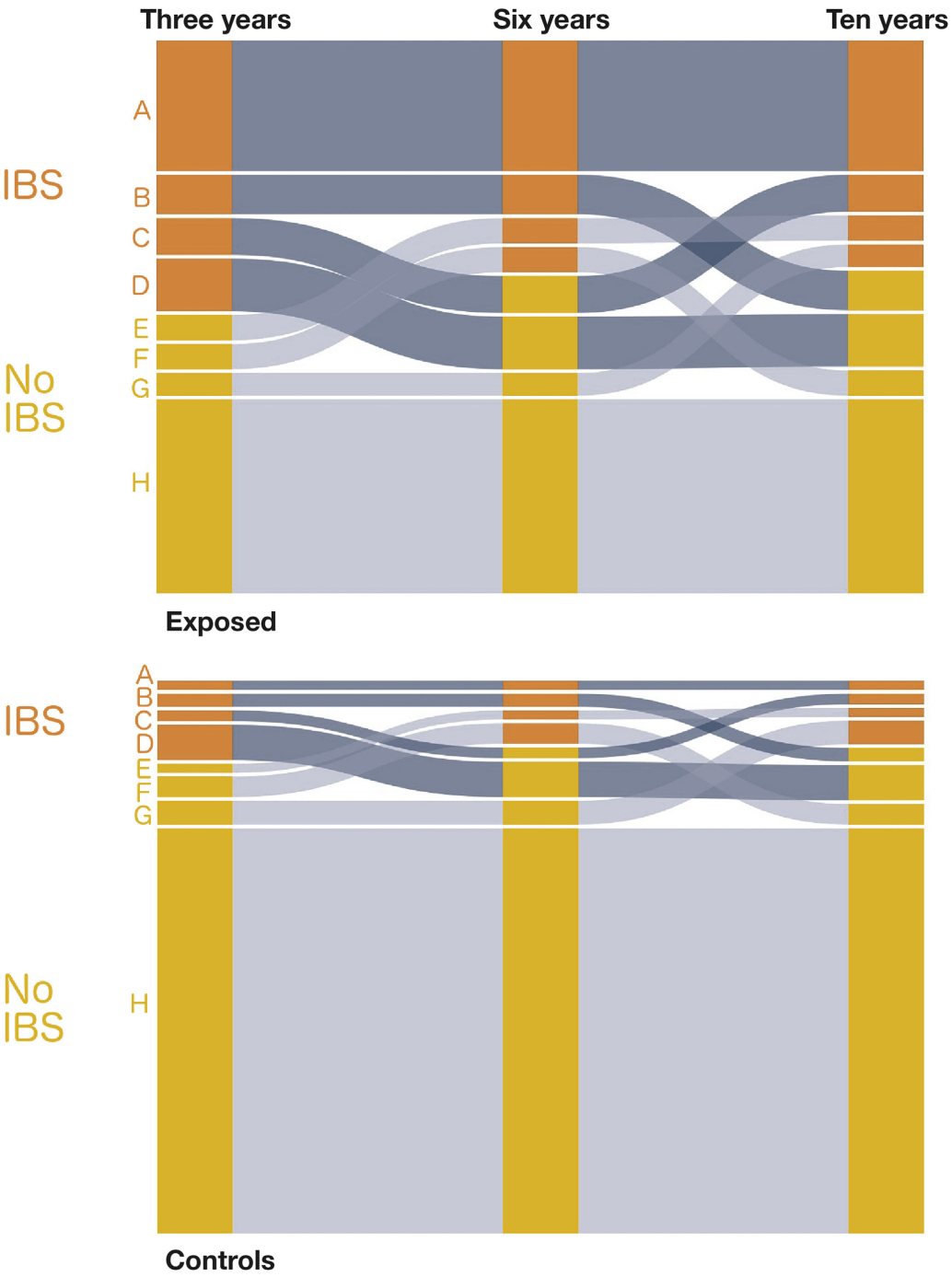

Figure 1. The contents of Table 5 visualized as Sankey diagrams. Letters A–H in Table 5 correspond to lines A–H in the figure graphic. The thickness of the lines corresponds to the proportion of that particular group relative to the population of 399 for the exposed group and 356 for the control group.

Table 2. Demographics of the Analyzed Cohorts 10 Years After a *Giardia lamblia* Outbreak in Bergen, Norway, 2004

	Respondents who answered at 10-year follow-up n = 1286					Respondents who answered at all follow-ups n = 792				
	Exposed		Control subjects			Exposed		Control subjects		
Characteristics	n = 590	%[a]	n = 696	%[a]	*P* Value[b]	n = 427	%[a]	n = 365	%[a]	*P* Value[b]
Female	395	66.9	455	65.4	.55	292	68.4	243	66.6	.59
Age										
Mean or range, *y*	42.9[c]	18–88[d]	43.6[c]	18–89[d]	.36	44.0[c]	18–88[d]	44.9[c]	20–83[d]	.31
0–19 *y*	5	0.8	2	0.3	.65	2	0.5	0	0	.48
20–39 *y*	294	49.8	335	48.1		199	46.6	157	43.0	
40–59 *y*	216	36.6	263	37.8		165	38.6	153	41.9	
60–79 *y*	69	11.7	87	12.5		55	12.9	52	14.2	
80–99 *y*	6	1.0	9	1.3		6	1.4	3	0.8	
Marital status					.04					.03
Single	124	21.1	113	16.3		88	20.7	50	13.7	
Married	423	71.9	536	77.1		308	72.5	292	80.0	
Divorced	35	6.0	32	4.6		24	5.6	15	4.1	
Widowed	6	1.0	14	2.0		5	1.2	8	2.2	
Education					.31					.96
Primary school	23	3.9	31	4.5		16	3.8	14	3.9	
Secondary school	128	21.9	172	25.1		90	21.2	79	22.0	
University	434	74.2	481	70.3		318	75.0	266	74.1	
Main occupation					.30					.90
Worker	478	81.2	580	83.6		352	82.6	300	82.2	
Student	16	2.7	16	2.3		8	1.9	9	2.5	
Unemployed/retired	78	13.2	88	12.7		57	13.4	50	13.7	
Other	17	2.9	10	1.4		9	2.1	6	1.6	

[a]Percentages may not total to 100 because of rounding.
[b]Pearson's chi-square exact 2-sided, except for sex (Fisher's exact 2-sided mid-*P*) and continuous age (Gosset's *t* test).
[c]Mean age.
[d]Age range.

10 years (aOR for the change 0.40; 95% CI, 0.33–0.48) and from 6 (31%) to 10 (26%) years with an aOR of 0.74 (95% CI, 0.61–0.90). In the control cohort, there were no changes in prevalence of CF for any time period (Table 4). No interaction was found by sex or age on the time changes for either IBS or CF. The corresponding figures for the subgroup outcomes are presented in Table 4.

The main outcomes IBS and CF were dichotomous and were measured at 3 different time points. Hence, there were 8 possible trajectories for the subgroup of respondents (n = 755 for IBS, n = 770 for CF) who

Table 3. Prevalence and OR of IBS and CF With Subgroups and Combinations of the Conditions 10 Years After a *Giardia lamblia* Outbreak in Bergen, Norway, 2004

	All[a]	Exposed		Control subjects		Unadjusted		Adjusted[b]	
Condition	n = 1286	n = 590	%	n = 696	%	OR	95% CI	OR	95% CI
IBS	1261	248	43.1	94	13.7	4.75	3.62–6.25	4.74	3.61–6.23
Severe IBS[c]	1259	54	9.4	14	2.0	4.96	2.73–9.03	5.05	2.77–9.20
CF	1279	153	26.1	73	10.5	2.99	2.20–4.05	3.01	2.22–4.08
Severe CF[d]	1279	43	7.3	9	1.3	6.00	2.90–12.41	5.98	2.89–12.39
IBS and CF	1255	101	17.6	19	2.8	7.44	4.49–12.32	7.46	4.51–12.36
IBS only	1255	146	25.4	75	11.0	2.76	2.03–3.74	2.74	2.02–3.72
CF only	1255	45	7.8	51	7.5	1.05	0.69–1.60	1.05	0.69–1.59

CI, confidence interval; CF, chronic fatigue; IBS, irritable bowel syndrome; OR, odds ratio.
[a]Number of cases with valid data for the outcome.
[b]Adjusted for sex and age in a multiple logistic regression model.
[c]IBS limiting activities at least often was defined as severe IBS.
[d]CF with a fatigue score of 23 or more was defined as severe CF.

Table 4. Changes in Prevalence of IBS and CF With Subgroups and Combinations of the Conditions 3, 6, and 10 Years After a *Giardia lamblia* Outbreak in Bergen, Norway, 2004

	Exposed								Control subjects						
	3 Years		6 Years		10 Years	% Change, adjusted[a] OR for change 6–10 years			3 Years		6 Years		10 Years	% Change, adjusted[a] OR for change 6–10 years		
Condition	n = 802, %		n = 731, %		n = 590, %	%	OR	95% CI	n = 843, %		n = 852, %		n = 696, %	%	OR	95% CI
IBS	354	46.7	288	39.8	248	43.1	3.3	1.03	0.87 to 1.22	116	14.0	98	11.6	94	13.7	2.1	1.13	0.87 to 1.47
Severe IBS	106	14.1	52	7.2	54	9.4	2.2	1.27	0.93 to 1.75	20	2.4	17	2.0	14	2.0	0.0	0.87	0.38 to 1.99
CF	366	46.9	224	31.3	153	26.1	–5.2	0.74	0.61 to 0.90	96	11.5	95	11.2	73	10.5	–0.7	0.93	0.70 to 1.24
Severe CF	120	15.4	66	9.2	43	7.3	–1.9	0.77	0.56 to 1.05	17	2.0	23	2.7	9	1.3	–1.4	0.42	0.21 to 0.85
IBS and CF	217	29.2	134	18.9	101	17.6	–1.3	0.84	0.66 to 1.07	35	4.2	28	3.3	19	2.8	–0.5	0.77	0.43 to 1.35
IBS only	127	17.1	148	20.9	146	25.4	4.5	1.25	0.99 to 1.58	80	9.7	69	8.2	75	11.0	2.8	1.28	0.93 to 1.76
CF only	124	16.7	86	12.1	45	7.8	–4.3	0.65	0.47 to 0.91	61	7.4	64	7.6	51	7.5	–0.1	0.99	0.70 to 1.39

CI, confidence interval; CF, chronic fatigue; IBS, irritable bowel syndrome; OR, odds ratio.
[a]Adjusted for sex and age in a multiple logistic regression model.

answered at all time points and were not missing for the variables of interest (Table 5 and Figure 1 for IBS and Supplementary Table 3 with figure for CF). Persistent IBS was more common among exposed (99 of 399, 25%) than among control subjects (6 of 356, 1.7%) with an aOR for persistent IBS among the exposed of 19.3 (95% CI, 8.3–44.7). Persistent CF was reported among 57 of 406 (14%) of the exposed and 3 of 364 (0.82%) of the control subjects with an aOR for CF among exposed of 20.5 (95% CI, 6.3–66.2).

The prevalence of IBS subtypes among the 248 exposed individuals with IBS after 10 years was 11% for IBS with constipation, 44% for IBS with diarrhea, 38% for mixed subtype, and 7% for unsubtyped. Corresponding numbers for 3- and 6-year follow-ups are available as Supplementary Table 4. IBS subtype was stable over time in 33 of 99 exposed individuals with persisting IBS (33%) whereas the rest shifted between the 4 subtypes between follow-ups (see Supplementary Tables 5 and 6 for details).

Discussion

The main finding in this study was that the prevalence and odds ratio of both IBS and CF remained high 10 years after the acute giardiasis. The prevalence of IBS decreased from 3 to 6 years and 3 to 10 years after exposure, while there was no change from 6 to 10 years. The prevalence of CF fell over the 3 time points. *Giardia* exposure was strongly associated with persistence of IBS and CF.

Strengths and Limitations

A strength of this study was the fact that all participants in the exposed cohort had a laboratory-defined diagnosis of giardiasis during a verified outbreak, which is not always the case in studies of PI-IBS.[5] Possible coinfection with other pathogens has not systematically been ruled out in this cohort, but we consider the risk of coinfection to be low. Robertson et al[22] found clinically significant coinfection with *Cryptosporidium parvum* unlikely. Further, this was a well-defined outbreak where an unspecified number of the first patients from the outbreak had been investigated for bacterial gastroenteritis in accordance with the local laboratory's standard panel with a negative result. The contaminated drinking water was purified by chlorination, which is effective against bacteria, but not *Giardia*.[15] Despite a decreased response rate after 10 years, our study cohorts still had a high number of participants (590 for exposed individuals, 696 for control subjects), which increased the power of the study. As 427 exposed and 365 control subjects answered at all follow-up times, this study represented a unique opportunity to follow the natural course of the conditions IBS and CF over

Table 5. Persistent, Incident and Recovered IBS After the 2004 *Giardia lamblia* Outbreak in Bergen, Norway Among Cases Who Answered at All Follow-Ups (3, 6, and 10 Years After Exposure) and Are Nonmissing for the Variable IBS, n = 755

	Group	Years after exposure			Exposed		Control subjects	
		3	6	10	n	%	n	%
A	IBS persistent	IBS	IBS	IBS	99	24.8	6	1.7
B	IBS recovered after 10 years	IBS	IBS	No	30	7.5	9	2.5
C	IBS after 3 and 10 years	IBS	No	IBS	28	7.0	7	2.0
D	IBS recovered after 6 years	IBS	No	No	40	10.0	24	6.7
E	IBS incident after 6 years	No	IBS	IBS	19	4.8	6	1.7
F	IBS incident after 6, recovered after 10 years	No	IBS	No	19	4.8	14	3.9
G	IBS incident after 10 years	No	No	IBS	17	4.3	16	4.5
H	Never IBS	No	No	No	147	36.8	274	77.0
	Total				399	100.0	356	100.0
	Total prevalence of IBS in exposed group per year, %[a]	49.4	41.9	40.9				
	Total prevalence of IBS in control group per year, %[a]	12.9	9.8	9.8				

IBS, irritable bowel syndrome.
[a]Sum of the 4 upper red boxes in Figure 1 each year.

time, as presented in the Sankey-diagrams (Table 5 with Figure 1 and Supplementary Table 3 with figure).

The response rate in the exposed cohort declined from 65% after 3 years (9) to 50% after 10 years, and selection bias cannot be ruled out. The subgroup of exposed who answered at all time points could possibly be more selected than the exposed group as a whole. However, this group had a prevalence of IBS and CF comparable to the whole group. In a simulated scenario with maximum bias in the exposed group (Supplementary Table 2) we found that both IBS and CF were still associated with exposure 10 years after infection (ORs, 1.7 and 1.3, respectively). This finding strengthens the conclusions of the current study. The predominance of women in the exposed group has been explained in part by women drinking more tap water, increasing the probability of clinical infection.[15] The fact that the prevalence of IBS and CF remained largely unchanged at all time points in the control group at a level that is comparable to the Norwegian normal population[23,24] suggests that selection bias is not a major problem in the control group.

Baseline information about respondents in this study was not available, including preoutbreak prevalence of IBS, psychological profile, and other comorbidities. Three studies from this outbreak have addressed the issue of preoutbreak abdominal symptoms, without clear evidence of an association between pre-existing abdominal complaints and postinfectious complications.[9]

The control group was recruited from the same area as the outbreak, and hence we included a question to exclude control subjects who self-reported a physician-verified diagnosis of giardiasis in 2004. This reduced the probability of including control subjects with clinical giardiasis, which could have led to an underestimation of the association between *Giardia* exposure and the outcomes.

Interpretation

The prevalence of IBS among the exposed (43%) in our study 10 years after the acute infection is high compared with other studies on PI-IBS. One review found a range of prevalence of PI-IBS after epidemic infections between 7% and 36%, where all the studies included had a shorter follow-up time than 10 years.[5] This unexpectedly high prevalence of IBS after 10 years could be partly explained by a general increase in diagnoses of functional bowel diseases in the society as a whole due to increasing awareness of these conditions in the population. There was a time lag before the outbreak was recognized,[15] and some patients probably had giardiasis for some time before they received treatment, possibly increasing the risk for developing PI-IBS. Previous studies have concluded that chronic giardiasis or lactose-intolerance cannot explain the high prevalence of IBS in this cohort.[9,25] Due to the heterogeneity among studies on PI-IBS, direct comparisons of the results are challenging. We found a strong association between *Giardia* exposure and IBS 10 years after exposure. A recently published 10-year follow-up study found a significant association between exposure to shigellosis and PI-IBS 1 and 3 years after the infection, but no significant association 5, 8, or 10 years later.[7] The Walkerton outbreak had a follow-up time of 8 years, and found that exposure to a mixture of bacterial pathogens was associated with PI-IBS 8 years after exposure, with a prevalence of PI-IBS among exposed of 15.4%.[6] Previous research has suggested that bacterial pathogens cause

longer lasting symptoms of PI-IBS than viral pathogens.[10] Our findings suggest that PI-IBS after infection with the parasite *Giardia* may have a poorer prognosis than after both bacterial and viral infections.

Other studies have found younger age and female sex to be risk factors for the development of PI-IBS following infection,[10] but we did not replicate this finding among the exposed in our study. Female sex is also known as a risk factor for IBS among sporadic cases.[26] We found that significantly more women than men had IBS in the control group, but no sex difference in the exposed group. This possible interaction of sex on exposure effect on IBS was not statistically significant when performing the Breslow-Day test.

Before the 2004 *Giardia* outbreak in Bergen, few studies had investigated long-term associations between gastrointestinal infection and CF. Previous studies on postinfectious fatigue are heterogeneous, and the definition of CF varies. Some studies[12] have investigated CFS, not to be confused with CF as defined in our study. With these limitations in mind, it nevertheless seems clear that postinfectious CI is a condition[8,11–14] to be considered in the clinic, and our study adds evidence to this. While the prevalence of IBS among the exposed in our cohort fell somewhat from 3 to 6 years but then seemed to plateau at a high prevalence, CF after *Giardia* infection seemed to have a better prognosis, as the prevalence fell also from 6 to 10 years after acute giardiasis. The difference in prognosis could partly be due to different therapeutic interventions received during follow-up, but our questionnaire did not assess this.

From Table 5 and Figure 1 it is clear that there was a considerable change to and from the criteria-based IBS diagnosis among both the exposed and the control group from time point to time point. This probably reflects some of the true incident and recovered cases of IBS over a time span, but it could also reflect the fact that although IBS is considered a chronic condition, it is also a condition that has fluctuating symptoms over time.[26] The stability of the IBS subtype among exposed with persisting IBS was also low, in line with the findings from the 8-year follow-up of the Walkerton outbreak.[6] Interestingly, there was a strong association between exposure and persistent IBS (IBS criteria met at all 3 follow-ups). This may be due to the fact that respondents in the exposed group on average probably had a closer relation in time to at least 1 possible IBS causing factor (*Giardia* exposure), than the control group, whose IBS causing factor(s) were unknown.

Through follow-up of a cohort of laboratory verified *Giardia* exposed and their controls at 3, 6, and 10 years after exposure, we now have more knowledge about the natural history of long-term complications after this infection. IBS and CF both remained associated with exposure even 10 years after the acute infection. The prevalence of CF fell through all follow-ups, whereas the IBS prevalence reached a plateau after an initial fall in prevalence. Clinicians need to consider both these conditions when a patient with a known history of gastrointestinal infection presents with unexplained symptoms even long after the acute infection is resolved.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.01.022.

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Conflicts of interest
This author discloses the following: Kurt Hanevik has served on an advisory board for Lupin Pharmaceuticals. The remaining authors disclose no conflicts.

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Methods

Supplementary Text. Selection Bias Analyses

Selection bias was assessed in 2×2 tables with stratification. Response/no response after 10 years was the outcome, and CF and IBS after 3 and 6 years, respectively, were the independent variables. The analyses were stratified according to status as exposed or controls. A scenario with maximum bias in the exposed group was simulated with the prevalence of either outcome set to be zero among nonresponders, whereas control group nonresponders were included with an assumed prevalence identical to that among control group responders. These results were not adjusted, as nonresponder responses were imputed.

Results

A higher proportion among exposed with IBS after 3 years (68%) than among exposed without IBS (60%) responded to the 10-year follow-up (OR for response after 10 years 1.4; 95% CI: 1.1 to 2.0). Among exposed with IBS after 6 years 71% responded after 10 years as compared to 64% among exposed without IBS (OR for response after 10 years 1.4; 95% CI: 1.0 to 1.9). Among controls no differences were found in response rate after 10 years dependent on IBS-status after 3 or 6 years. There were no changes in response rates at 10 years among exposed after 3 or 6 years according to CF-status. Controls with CF after 3 years were less likely to respond after 10 years than controls without CF (46% vs. 58%, OR for response after 10 years 0.61 CI: 0.40 to 0.95), but there was no change in response rates according to CF-status after 6 years (Supplementary Table 1). A scenario with maximum bias in the exposed group resulted in an OR for IBS of 1.7 (95% CI 1.4 to 2.1) and for CF of 1.3 (95% CI 1.0 to 1.6) (Supplementary Table 2).

Supplementary Table 1. Cross-Tabulations on Whether Study Participants Responded or Not After 10 Years Dependent on Response to Question on IBS/CF or Not After 3 and 6 Years, Stratified to Exposure Status

				Responders After 10 Years			
Answer After	Cohort	Condition		%	n/n	OR[a]	95% CI
3 y	Exposed	IBS	Yes	68	235/344	1.44	1.06 to 1.95
			No	60	235/392		
	Controls		Yes	55	62/113	0.92	0.62 to 1.37
			No	57	393/690		
	Exposed	CF	Yes	62	220/353	0.96	0.71 to 1.29
			No	63	256/404		
	Controls		Yes	46	42/92	0.61	0.40 to 0.95
			No	58	417/721		
6 y	Exposed	IBS	Yes	71	202/285	1.39	1.00 to 1.91
			No	64	274/430		
	Controls		Yes	60	58/96	1.08	0.70 to 1.67
			No	59	430/735		
	Exposed	CF	Yes	66	146/221	0.95	0.68 to 1.33
			No	67	327/487		
	Controls		Yes	54	50/93	0.78	0.51 to 1.21
			No	60	442/740		

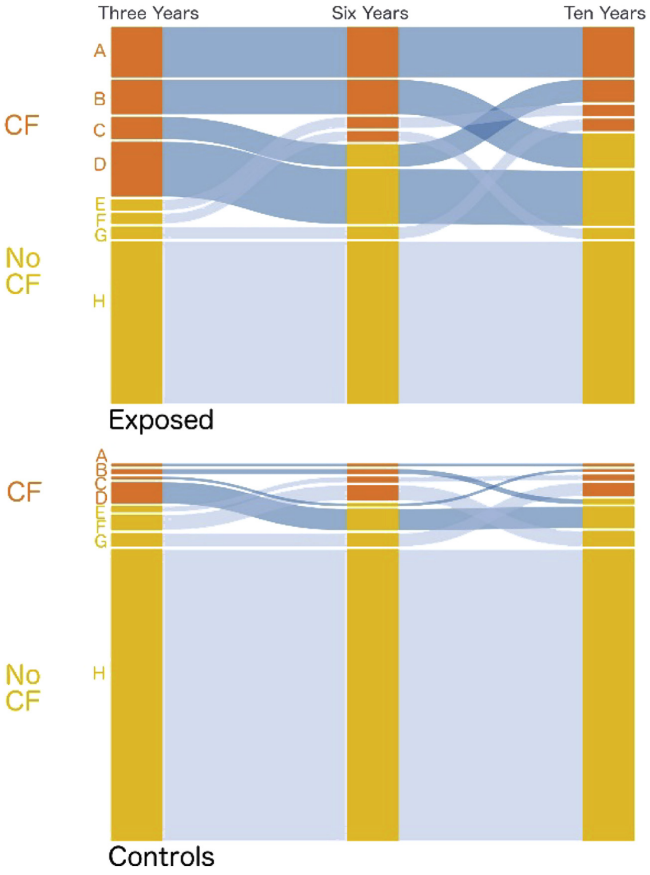
CI, confidence interval; CF, chronic fatigue; IBS, irritable bowel syndrome; OR, odds ratio.
[a]Breslow-Day test for homogeneity of OR (exposed/controls) was negative ($P > .05$) for all outcomes.

Supplementary Table 2. Results From Cross-Tabulation Analyses of IBS or CF According to Exposure Status in a Scenario With Maximum Bias in the Exposed Group[a]

Condition	Group	%	n	N	OR	95% CI
IBS	Exposed	21.4	248	1160	1.71	1.43 to 2.06
	Controls	13.7	316	2307		
CF	Exposed	13.1	153	1171	1.28	1.03 to 1.59
	Controls	10.5	243	2314		

CI, confidence interval; CF, chronic fatigue; IBS, irritable bowel syndrome; OR, odds ratio.
[a]A scenario with maximum bias in the exposed group was simulated with the prevalence of either outcome set to be zero among nonresponders, whereas control group nonresponders were included with an assumed prevalence identical to that among control group responders.

Supplementary Table 3 with Figure. Persistent, Incident, and Recovered CF After the 2004 *Giardia lamblia* Outbreak in Norway Among Cases Who Answered at All Follow-Ups (3, 6, and 10 Years After Exposure) and Are Nonmissing for CF (n = 770) . The Thickness of the Lines in the Figure Graphic Correspond to the Proportion of That Particular Group Relative to the Population of 406 for the Exposed Group and 364 for the Control Group



	Group	Years after exposure			Exposed		Controls	
		3	6	10	n	%	n	%[a]
A)	CF persistent	CF	CF	CF	57	14.0	3	0.8
B)	CF recovered after 10 years	CF	CF	No	39	9.6	5	1.4
C)	CF after 3 and 10 years	CF	No	CF	25	6.2	3	0.8
D)	CF recovered after 6 years	CF	No	No	62	15.3	22	6.0
E)	CF incident after 6 years	No	CF	CF	13	3.2	6	1.6
F)	CF incident after 6 years, recovered after 10 years	No	CF	No	12	3.0	16	4.4
G)	CF incident after 10 years	No	No	CF	14	3.4	14	3.8
H)	Never CF	No	No	No	184	45.3	295	81.0
	Total				406	100.0	364	99.8
	Total prevalence of CF in exposed group per year, %[b]	45.1	29.8	26.8				
	Total prevalence of CF in control group per year, %[b]	9.1	8.2	7.1				

CF, chronic fatigue; No, no chronic fatigue.
[a]Percentages did not total to 100 because of rounding.
[b]The sum of the 4 upper red boxes (CF) each year.

Supplementary Table 4. Prevalence of IBS Subtype Per Year Among Those Exposed With IBS After an Outbreak of Giardiasis in Bergen, Norway, 2004

	Years after exposure					
	3		6		10	
IBS Subtype[a]	n	%[b]	n	%[b]	n	%[b]
Constipation	34	9.6	35	12.2	26	10.5
Diarrhea	137	38.7	108	37.5	109	44.0
Mixed	161	45.5	118	41.0	95	38.3
Unsubtyped	22	6.2	27	9.4	18	7.3
Total	354	100	288	100.1	248	100.1

IBS, irritable bowel syndrome.
[a]Defined according to the Rome III criteria.
[b]Percentages may not total to 100 because of rounding.

Supplementary Table 5. Shifts in IBS Subtype Per Year Among Those Exposed With Persisting IBS (n = 99) After an Outbreak of Giardiasis in Bergen, Norway, 2004

Years after exposure				
3	6	10	n	%[a]
C	C	C	4	4
C	M	C	1	1
C	D	D	2	2
C	C	M	2	2
C	M	M	2	2
D	M	C	2	2
D	C	D	1	1
D	D	D	17	17
D	M	D	3	3
D	C	M	1	1
D	D	M	5	5
D	M	M	1	1
M	M	C	2	2
M	D	D	9	9
M	M	D	8	8
M	D	M	6	6
M	M	M	12	12
X[b]	X[b]	X[b]	21	21
		Total	99	99

C, constipation; D, diarrhea; IBS, irritable bowel syndrome; M, mixed; U, unsubtyped.
[a]Percentages may not total to 100 because of rounding.
[b]IBS subtype is a 4-level variable. With 3 follow-ups, there are $4 \times 4 \times 4 = 64$ possible trajectories. We therefore collapsed all trajectories containing at least 1 instance of the category unsubtyped.

Supplementary Table 6. Shifts in IBS Subtype Among Those Exposed With Persisting IBS (N = 99) After an Outbreak of Giardiasis in Bergen, Norway, 2004

Type of trajectory[a]	n	%[b]
Flow between C and D[c]	6	6
Flow between M and D[d]	32	32
Flow between M and C[e]	7	7
Stable C	4	4
Stable D	17	17
Stable M	12	12
Contains unsubtyped[f]	21	21
Total	99	99

C, constipation; D, diarrhea; IBS, irritable bowel syndrome; M, mixed.
[a]The trajectories in Supplementary Table 5 have been collapsed.
[b]Percentages may not total to 100 because of rounding.
[c]Includes trajectories CDD, DCD, DMC, DCM.
[d]Includes trajectories DMD, DDM, DMM, MDD, MMD, MDM.
[e]Includes trajectories CMC, CCM, CMM, MMC.
[f]Includes all trajectories containing at least 1 instance of category unsubtyped.

PAPER 3

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ORIGINAL ARTICLE

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Quality of life and its association with irritable bowel syndrome and fatigue ten years after giardiasis

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Abstract

Background: Gastroenteritis has been associated with complications such as irritable bowel syndrome (IBS) and chronic fatigue (CF). Little is known about the implications for quality of life (QoL) in this setting. The aims of this study were to evaluate the association between exposure to *Giardia* infection and QoL ten years after the infection, and how this related to IBS and CF.

Methods: We followed 1252 patients with laboratory-verified *Giardia lamblia* infection and a matched control group for 10 years after an epidemic in Bergen, Norway, in 2004. The main outcome was QoL after ten years as defined by the Short-form 12 version 2 with a physical component summary (PCS) and a mental component summary (MCS), both with range 0-100 (T-score). Regression analyses were performed using mixed modeling.

Key Results: Mean PCS T-score in the exposed group (51.4; 95% CI: 50.6-52.1) was 2.8 T-score points (95% CI: −3.8 to −1.9, $P < 0.001$) lower than that in the control group (54.2; 95% CI: 53.7-54.8). The mean MCS T-score was also 2.8 T-score points (95% CI: −3.8 to −1.9, $P < 0.001$) lower among the exposed (48.9; 95% CI: 48.2-49.6) than the controls (51.7; 95% CI: 51.1-52.4). Further analyses found that the effect of *Giardia* exposure on QoL was mediated by IBS and CF.

Conclusions & Inferences: Exposure to *Giardia* infection was associated with a lower QoL ten years later as compared to a control group, an effect that was mediated by IBS and CF.

KEYWORDS
epidemiology, infectious disease, Irritable bowel syndrome, quality of life

1 | INTRODUCTION

Gastrointestinal infections can lead to long-term complications after the microbial agent has been eradicated. Post-infectious irritable bowel syndrome (PI-IBS) has been recognized for decades[1] and is clinically similar to sporadic irritable bowel syndrome (IBS). Chronic fatigue syndrome (CFS) is another known condition following some infections,[2] including giardiasis.[3,4] Chronic fatigue (CF) is a useful and validated concept in epidemiologic studies where clinical examination is not feasible.[5] CF has also been found to be a long-lasting

Abbreviations: CF, chronic fatigue; CFS, chronic fatigue syndrome; CI, confidence interval; IBS, irritable bowel syndrome; MCS, mental component summary; OR, odds ratio; PCS, physical component summary; QoL, Quality of life; SD, Standard deviation; SF-12v2, Short-form 12 version 2.

complication after giardiasis.[6–8] Few studies have investigated quality of life (QoL) after gastrointestinal infections. One study found that QoL was impaired six months after *Shiga* toxin-producing *Escherichia coli* gastroenteritis, and that the physical QoL normalized after one year, whereas the mental QoL remained impaired.[9] CFS and IBS have been shown to affect QoL.[10-14]

In 2004, one of the main drinking-water reservoirs of the city of Bergen, Norway, was contaminated by *Giardia lamblia* cysts. IBS and CF were associated with exposure to *Giardia* infection as long as ten years after the outbreak,[6] but how this may affect QoL is not well known. The main aim of this study was to evaluate the association between exposure to *Giardia* infection and QoL ten years after the Bergen outbreak, as compared to a control group. The secondary aim was to assess how QoL related to IBS and CF in the exposed and the control group.

Key Points

- Irritable bowel syndrome (IBS) and fatigue are known complications following gastroenteritis. This paper assessed the quality of life ten years after a *Giardia lamblia* gastroenteritis and how this related to IBS and fatigue.
- Quality of life was lower among patients who suffered from gastroenteritis, mainly due to the development of IBS and fatigue.
- Clinicians should be aware that gastroenteritis can have a lasting impact on quality of life in patients, especially in those who have long-term complications.

2 | MATERIALS AND METHODS

2.1 | Design and participants

This was a prospective cohort study following 1252 infected patients with laboratory-verified *Giardia lamblia* (the exposed group) and a control group three, six, and ten years after an epidemic of giardiasis in Bergen, Norway, 2004. The group of 2504 controls was matched 2:1 by sex and age to the exposed group and was recruited from the Bergen area by Statistics Norway, on our request. We only included participants who were 18 years or older in 2014 for this study.

Patients consented to participate upon answering the questionnaire. The Regional Committee for Ethics in Medical Research approved the study (ref.no. 2014/1372).

2.2 | Variables

Health-related QoL was the main outcome of the study, as measured by the Short-form 12 version 2 (SF-12v2). The SF-12v2 consists of a physical component summary (PCS) and a mental component summary (MCS), measuring physical and mental QoL, respectively. The PCS and MCS range from 0-100 and are based on a 2009 US norm for QoL with a mean of 50 and a standard deviation of 10. The points on the scale are referred to as T-score points. The two scores are based on the score of eight sub-scales, that is, physical functioning, role-physical (how the physical QoL affects daily functioning), bodily pain, general health, vitality, social functioning, role-emotional (how the mental QoL affects daily functioning), and mental health. Although all eight sub-scales contribute to the scoring of both PCS and MCS, the former three have the strongest correlation with PCS, and the latter three have the strongest correlation with MCS. Also, the use of an orthogonal scoring algorithm applies negative weights to sub-scales most strongly correlated with MCS when scoring the PCS (and vice versa), ensuring validity in discriminating between physical and mental health outcomes. In addition, PCS and MCS scores were both dichotomized based on a score of 45 and above, or lower than 45. Scoring of the QoL variables was done using the QualityMetric Health Outcomes™ Scoring Software 5.0, as recommended by the developers of the SF-12.[15] The software's option to estimate missing scores was used. We used PCS and MCS means and standard deviations from Gandek et al[16] to compare our results with a Norwegian norm. The SF-12 was translated to Norwegian and validated for use on a Norwegian population as part of that study. The developers of the SF-12 suggest that when comparing QoL between groups, a difference in three or more T-score points is considered clinically important.[15]

IBS was defined according to the Rome-III criteria.[17] Respondents were defined as having IBS if reporting recurrent abdominal pain or discomfort for at least three days per month in the last three months, associated with at least two or more of the additional IBS-criteria related to defecation or stool changes, if onset of symptoms was at least 6 months prior to completing the questionnaire.

CF was defined using the Fatigue Questionnaire.[5] This validated questionnaire consists of 13 questions, where 11 of these measure different aspects of fatigue on a four-item Likert scale: "less than usual" (0), "as usual" (1), "more than usual" (2), and "much more than usual" (3). The sum of these scores constitutes the total fatigue score with a range of 0-33. The Likert scale scores are also dichotomized (0 and 1 into 0, 2 and 3 into 1), and CF is defined as a dichotomized score of four or more and a duration of six months or more. Cases with 4 or less missing answers on the 11 fatigue-related questions were included, and the missing responses for the questions were estimated based on the average for non-missing responses to that particular question.

IBS and CF were assessed at follow-ups of 3, 6, and 10 years after the outbreak, whereas QoL was assessed only at the 10-year follow-up.

To better assess and illustrate the relationships between exposure status, IBS and CF (all dichotomous), and the outcomes PCS and MCS, the three former variables were combined into one eight-category variable with the categories "Neither condition among controls" (reference category in regression analyses), "Neither condition among exposed", "IBS-only among controls", "IBS-only among exposed", "CF-only among controls", "CF-only

among exposed", "IBS and CF among controls", and "IBS and CF among exposed".

Demographic variables recorded were sex (dichotomous), age (continuous and categorized according to the SF12v2 user's manual[15]), marital status (four categories), level of education (three categories), and source of income (four categories).

2.3 | Analyses and statistical methods

We calculated descriptive statistics as percentage, mean, standard deviation (SD), and 95% confidence intervals (CI). We used Fisher's exact 2-sided mid-p test in 2 × 2 tables for binary outcomes[18] and Pearson's chi-square exact 2-sided test for multilevel outcomes.

To account for dependence between matched subjects, we used mixed modeling with unstructured covariance when performing regression analyses.

All means presented are the observed means, to give the reader the unadjusted values of PCS and MCS for the different study groups. All differences between means presented are estimated, as they are the results of regression analyses, and hence, they do not necessarily equal the crude differences between the observed means.

TABLE 1 Response rate, demographics, and prevalence of irritable bowel syndrome and chronic fatigue of the cohorts ten years after a *Giardia lamblia* outbreak in Bergen, Norway, in 2004

	Respondents who answered at ten-year follow-up, N = 1286				
	Exposed (n = 590)		Controls (n = 696)		
Characteristics	n	%[a]	n	%[a]	*P*-value[b]
Response rate	592/1176	50.3	708/2330	30.4	
Female sex	395	66.9	455	65.4	NA[c]
Age in years					
Mean/range	42.9[d]	18-88[d]	43.6[d]	18-89[d]	NA[c]
18-24	12	2.0	9	1.3	NA[c]
25-34	174	29.5	184	26.4	
35-44	189	32.0	258	37.1	
45-54	103	17.5	98	14.1	
55-64	72	12.2	88	12.6	
65-74	32	5.4	44	6.3	
75-89	8	1.4	15	2.2	
Marital status					
Single	124	21.1	113	16.3	0.04
Married	423	71.9	536	77.1	
Divorced	35	6.0	32	4.6	
Widowed	6	1.0	14	2.0	
Education					
Primary school	23	3.9	31	4.5	0.31
Secondary school	128	21.9	172	25.1	
University	434	74.2	481	70.3	
Main occupation					
Worker	478	81.2	580	83.6	0.30
Student	16	2.7	16	2.3	
Unemployed/ retired	78	13.2	88	12.7	
Other	17	2.9	10	1.4	
IBS prevalence	248	43.1	94	13.7	<0.001
CF prevalence	153	26.1	73	10.5	<0.001

CF, chronic fatigue; IBS, irritable bowel syndrome.
[a]Percentages may not total to 100 because of rounding.
[b]Pearson's chi-squared exact 2-sided, except for IBS and CF (Fisher's exact 2-sided mid-p).
[c]NA = not applicable; respondents were matched on sex and age, and hence, we did not perform significance testing for these variables.
[d]Mean age, age range.

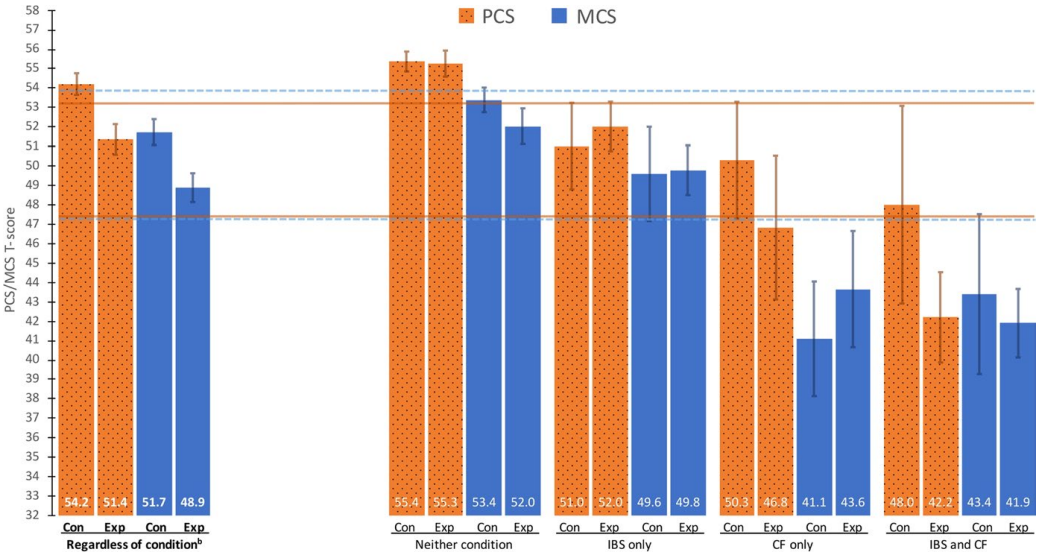

FIGURE 1 Observed mean PCS and MCS with 95% confidence intervals 10 years after a Giardia lamblia outbreak in Bergen, Norway, in 2004, as compared to a Norwegian Norm[a]. PCS, physical component summary; MCS, mental component summary; IBS, irritable bowel syndrome; CF, chronic fatigue; Con, controls; Exp, exposed to *Giardia*. [a]SF-12 scores for a Norwegian sample population from Gandek et al.[16] The horizontal lines on the figure are one-third of a standard deviation T-score points under/over the mean T-score from that population. Dotted for MCS, solid for PCS. [b]The first four columns (with bold labels) depict PCS and MCS according to exposure status. The next sixteen columns depict PCS and MCS according to the eight-category variable described in the methods section

Confounding was evaluated with regression analyses. Level of education, source of income, and marital status were considered potential confounders. Sex and age were matched for and hence were not considered potential confounders. Possible interactions from IBS, CF, sex, or age on the effect of exposure on PCS and MCS were evaluated in the regression models and with the Breslow-Day test for homogeneity of the OR in stratified cross-tabulations.

All tests were two-sided with the level of statistical significance set to 0.05. The analyses were done using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, USA).

3 | RESULTS

Response rate, demographic data, prevalence of IBS and CF, and non-responder analyses of this cohort ten years after the *Giardia* outbreak have been published previously,[6] and some of these data are summarized in Table 1. For PCS, there were 0.3% missing values among exposed (2/590) and 0.9% missing among controls (6/696). For MCS, there were no missing values. For IBS, there were 14 missing out of 590 (2.4%) among exposed and 11 of 696 (1.6%) among controls. For CF, the corresponding numbers were 3/590 (0.5%) and 4/696 (0.6%), respectively.

Mean QoL T-score for the entire cohort regardless of group was 52.9 (SD: 8.7) for PCS and 50.4 (SD: 9.1) for MCS.

Mean PCS T-score in the exposed group (51.4; 95% CI: 50.6-52.1) was 2.8 T-score points (95% CI: −3.8 to −1.9; $P < 0.001$) lower than for the control group (54.2; 95% CI: 53.7-54.8). The mean MCS T-score was also 2.8 T-score points (95% CI: −3.8 to −1.9, $P < 0.001$) lower among the exposed (48.9; 95% CI: 48.2-49.6) than the controls (51.7; 95% CI: 51.1-52.4; Figure 1).

"Neither condition among controls" (after ten years) was the reference category in regression analyses and was the subgroup with the highest QoL for both PCS and MCS (Tables 2 and 3), with mean T-scores of 55.4 (95% CI: 54.9-55.9) and 53.4 (95% CI: 52.8-54.0), respectively. The exposed with neither condition after ten years had the same PCS (mean T-score difference: −0.1; 95% CI: −1.2 to 1.0; *P*-value: 0.84), but a lower MCS (mean T-score difference: −1.4; 95% CI: −2.5 to −0.2; *P*-value: 0.023) than the reference category. All other categories in the eight-category variable described in the methods section had a lower QoL than the reference category, both for PCS and for MCS. This eight-category variable was also analyzed with PCS and MCS as a dichotomized outcome with a T-score below 45 points or not (Tables 2 and 3). Over 50% of the respondents in the category "IBS and CF among exposed" had a PCS lower than 45 points. For MCS, all categories comprising respondents with CF-only or CF and IBS had over 50% of respondents with an MCS score below 45.

In a regression model with exposure status, IBS and CF after ten years as independent variables, and PCS as the outcome, there was

TABLE 2 Quality of life, physical component summary analyzed by simple regression analyses, as continuous and dichotomized variable according to exposure group 10 years after a *Giardia lamblia* outbreak in Bergen, Norway, in 2004 (N = 1247)

					PCS score below 45			
Exposure group	N	Mean/difference	95% CI for mean/ difference	*P*-value	n	%	OR	95% CI
Neither condition among controls	532	55.4[a]	54.9 to 55.9	ref	35	6.6	ref	ref
Neither condition among exposed	280	−0.1	−1.2 to 1.0	0.84	18	6.4	1.0	0.6-1.8
IBS-only among controls	75	−4.4	−6.2 to −2.5	<0.001	17	22.7	4.4	2.3-8.3
IBS-only among exposed	146	−3.3	−4.7 to −1.9	<0.001	20	13.7	2.4	1.3-4.3
CF-only among controls	50	−5.1	−7.3 to −2.9	<0.001	16	32.0	6.1	3.0-12.2
CF-only among exposed	45	−8.6	−10.9 to −6.2	<0.001	22	48.9	14.0	7.1-27.6
IBS and CF among controls	18	−7.5	−11.0 to −3.9	<0.001	6	33.3	6.9	2.4-20.2
IBS and CF among exposed	101	−13.1	−14.8 to −11.5	<0.001	55	54.5	17.4	10.3-29.5

CF, chronic fatigue; IBS, irritable bowel syndrome; PCS, physical component summary; Ref, reference group.
[a]Mean in reference group of eight-category exposure variable.

TABLE 3 Quality of life, mental component summary analyzed by simple regression analyses, as continuous and dichotomized variable according to exposure group ten years after a *Giardia lamblia* outbreak in Bergen, Norway, in 2004, (N = 1255)

					MCS score below 45			
Exposure group	N	Mean/difference	95% CI for mean/ difference	*P*-value	n	%	OR	95% CI
Neither condition among controls	536	53.4[a]	52.8 to 54.0	ref	67	12.5	ref	ref
Neither condition among exposed	282	−1.4	−2.5 to −0.2	0.023	50	17.7	1.6	1.0-2.3
IBS-only among controls	75	−3.8	−5.8 to −1.8	<0.001	15	20.0	1.7	0.9-3.3
IBS-only among exposed	146	−3.6	−5.1 to −2.1	<0.001	33	22.6	2.1	1.3-3.3
CF-only among controls	51	−12.3	−14.7 to −10.0	<0.001	30	58.8	9.6	5.2-17.8
CF-only among exposed	45	−9.8	−12.2 to −7.3	<0.001	23	51.1	7.6	4.0-14.4
IBS and CF among controls	19	−10.1	−13.8 to −6.3	<0.001	13	68.4	15.9	5.9-43.1
IBS and CF among exposed	101	−11.5	−13.3 to −9.8	<0.001	62	61.4	11.4	7.1-18.4

CF, chronic fatigue; IBS, irritable bowel syndrome; MCS, mental component summary; Ref, reference group.
[a]Mean in reference group of eight-category exposure variable.

no longer a significant effect of exposure status on the outcome with a mean PCS that was 0.50 T-score points lower among the exposed (95% CI: −1.4 to 0.40; *P*-value: 0.28). The same was found for mean MCS, which was 0.75 T-score points lower among the exposed (95% CI: −1.7 to 0.22; *P*-value: 0.13).

We found a significant interaction between CF and exposure status on both measures of QoL (Table 4). The mean PCS among those with CF in the exposed group was −9.2 points lower than for respondents without CF, whereas for controls, the difference was −4.7 ($P < 0.001$). For MCS, the relationship was inverse: The mean MCS among those with CF in the control group was −10.9 T-score points lower than for respondents without CF, whereas for exposed, the difference was −8.0 (*P*-value: 0.027). We found no significant interaction between IBS and exposure on QoL (*P*-value: 0.78 for PCS; *P*-value: 0.34 for MCS).

We found no interactions of sex on the association between exposure and PCS (*P*-value: 0.16) or MCS (*P*-value: 0.39), nor of age on the same associations (*P*-values: 0.10 and 0.056, respectively).

We also analyzed how exposure status, IBS and CF after three and six years related to QoL after ten years (Table S1). We found that for the eight-category variable with "Neither condition among controls" at each follow-up as reference category, the findings (in terms of direction and statistical significance of the results) were similar to the results above (after ten years) with some exceptions. In addition to the category, "Neither condition among exposed" also the category "IBS-only among controls" after six years had the same PCS as the reference category. The categories "Neither condition among exposed" and "IBS-only among controls" after both three and six years had the same MCS after ten years as the reference category. Corresponding analyses on dichotomized PCS and MCS after

TABLE 4 Physical component summary and mental component summary according to chronic fatigue status at ten years follow-up, in exposed and control cohorts of the *Giardia lamblia* outbreak in Bergen, Norway, in 2004[a]

Outcome	Cohort	CF	n	Mean	95% CI for mean or difference		*P*-value for interaction[b]	Difference between differences[c]
					Lower	Upper		
PCS	Exposed	Yes	146	43.7	41.7	45.6	<0.001	−4.5
		No	426	54.2	53.5	54.8		
		Difference[d]		−9.2	−10.7	−7.7		
	Control	Yes	68	49.7	47.1	52.2		
		No	607	54.8	54.3	55.4		
		Difference[d]		−4.7	−6.6	−2.7		
MCS	Exposed	Yes	146	42.4	40.9	43.9	0.027	2.9
		No	428	51.3	50.5	52.0		
		Difference[d]		−8.0	−9.6	−6.4		
	Control	Yes	70	41.7	39.3	44.1		
		No	611	52.9	52.3	53.6		
		Difference[d]		−10.9	−12.9	−8.9		

CF, chronic fatigue; CI, confidence interval; MCS, mental component summary (0-100); PCS, physical component summary (0-100).
[a]In a linear regression model including the factors cohort (exposed/control), irritable bowel syndrome (yes/no), CF (yes/no), and the interaction term cohort ×CF.
[b]Interaction between cohort and CF on the outcomes PCS and MCS.
[c]The difference in quality of life between CF and no CF among exposed, minus that among controls.
[d]Means are observed, with CI. Differences are estimated in a mixed linear model and hence do not necessarily equal observed mean value for CF minus mean value for no CF.

three and six years are found in Table S2. The effect of exposure on QoL after ten years was absent when controlling for IBS and CF after three and six years in a regression model, with the exception of the analysis after 6 years, where MCS after ten years was significantly reduced when controlling for IBS and CF after 6 years. The interaction between exposure and CF on QoL was not found after three or six years (Table S3).

Scores on the sub-scales most strongly associated with MCS were assessed descriptively to further elucidate the above-mentioned interaction between exposure status and CF on QoL (Table S4). The "vitality" subdomain had the lowest score, but this was rather similar between exposed and controls with CF-only (mean T-score 38.1 vs 38.4). The subdomain "mental health" was lower among controls with CF-only (44.9) than among exposed with CF-only (48.2).

We found no confounding of our results by the demographic variables marital status, level of education, and source of income.

4 | DISCUSSION

We found a lower QoL among giardiasis-exposed persons ten years after the exposure, as compared to a control group. This effect of the exposure to giardiasis on QoL was mediated by IBS and CF. For the association between exposure and QoL, there was an interaction between CF and exposure, as the reduction of physical QoL due to CF was larger among exposed than controls. The opposite was found for mental QoL.

4.1 | Interpretation

We found that exposure to *Giardia lamblia* was associated with a lower QoL ten years later as compared to a control group. However, the difference between the exposed and the controls for both PCS and MCS at 2.8 T-score points was below the proposed threshold of 3 T-score points that is considered clinically significant. The mean PCS for the control cohort was higher than the norm for the Norwegian population, whereas the mean PCS among exposed and the mean MCS regardless of exposure group were clinically similar to this norm.[16] This may in part be explained by the fact that our study population is relatively young. There is a slight decrease in PCS with age in normal populations, whereas MCS increases somewhat.[16]

Exposed who had neither condition had a similar PCS to controls with neither condition, whereas the MCS was slightly lower for the exposed. However, both these groups had a QoL higher than or equal to a Norwegian population norm. We found a trend that the presence of IBS alone lowered the QoL in both the exposed and control group, but less than CF alone did. The lowest QoL was found among exposed with both IBS and CF, both for PCS (42.2) and for MCS (41.9), as well as for CF-only among controls, with an MCS of 41.1. The PCS at 42.2 is comparable to that found in other conditions such as type 2 diabetes and recent myocardial infarction.[19] The MCS scores in the two above-mentioned groups were lower than the cutoff at ≤42 T-score points used to classify people as being at risk for clinical depression in one study.[20] Respondents with IBS-only had a QoL comparable to a

Norwegian norm regardless of exposure status and comparable to a subgroup of IBS patients with low IBS-symptom severity and no comorbidities in another study on IBS and QoL.[10] The PCS of the respondents with IBS-only in our study is also comparable to that of a group of IBS non-consulters in a study by Rey et al,[21] whereas the MCS is higher in our group. This could be explained by the fact that we have subgrouped our respondents into neither condition, IBS-only, CF-only or a combination of the two conditions. The MCS among respondents with IBS dropped markedly when they have comorbid CF, to a level comparable to that of Rey et al's IBS non-consulters where CF comorbidity is unknown.

The fact that the effect of exposure status disappeared in multiple regression analysis with IBS and CF included in the model supports the choice of these conditions as clinically relevant markers of the consequences of the *Giardia* epidemic. IBS and CF can be seen as mediators of the effects of *Giardia* exposure on QoL.

We found an interaction by CF on the effects of exposure on QoL in that the reduction in PCS score among respondents due to CF was significantly larger among the exposed than among controls. For MCS, the relationship was opposite, the reduction was significantly larger among controls than the exposed with CF. A possible explanation for this could be that although both groups probably have a multifactorial cause for their CF, the respondents with CF among the exposed have a more specific organic etiology for their condition (ie, *Giardia)*, whereas among controls mental factors could be more important. This notion is supported by the fact that the subdomain "mental health" was lower among controls with CF-only, than among exposed with CF-only (Table S4).

4.2 | Strengths and Limitations

One strength of this study was that the use of a control group made the unfortunate event of an outbreak simulate a natural experiment. The number of participants in both groups was high, and all of the exposed had a laboratory-confirmed diagnosis. The longitudinal aspect of the study variables IBS and CF (measured after three, six, and ten years) makes causal inferences about the relationship between these conditions and QoL after ten years plausible. We used the validated SF-12 to measure generic QoL. We performed the scoring using the developers recommended algorithm, with the 2009 US norm. The fact that the measure is generic, widely used and has a standardized scoring algorithm, makes direct comparisons of our scores to other studies on various patient groups using the SF-12 or SF-36 possible.[15]

The response rate in the exposed group (50%) is a source of possible bias, but is deemed acceptable and as expected for this kind of survey.[22] The control group response rate is lower (30%), and we have made the case against selection bias in a previous study on the same cohort.[6] Also, recent research suggests that a declining response rate does not necessarily imply increasing bias in analyses of associations, although simple distributional data may suffer.[22]

The demographic variables recorded in our study (marital status, level of education, source of income) were measured after the exposure and hence could in part be affected by the exposure, making their role as confounders questionable.

QoL, IBS, and CF were all measured at the same time point, 10 years after the exposure. This makes inferences about the relationships between these outcomes less certain. We therefore included results from analyses of IBS and CF measured at timepoints three and six years after exposure and their effect on QoL after 10 years as well. In terms of direction of the effect and statistical significance, the results from these analyses were generally similar to our main findings, except for the fact that the interaction between CF and exposure on QoL was only found after 10 years. Nevertheless, we believe that the longitudinal analyses support the notion of IBS and CF as causes of reduced QoL and justify discussing the role of IBS and CF as mediators of the effect of exposure on QoL, as well as CF as an interacting variable on the association between exposure status and QoL.

5 | CONCLUSION

We found a lower QoL among the exposed 10 years after giardiasis as compared to a control group, and this was mediated by IBS and CF. There was furthermore a significant interaction of CF on the association between the exposure and QoL. The effect of having CF in reducing the physical QoL was larger among the exposed than among controls, whereas for mental QoL, the opposite was found. The findings in this study support the importance of investigating whether patients suffer from PI-IBS and CF after giardiasis, as these complications explain the reduced QoL in the exposed cohort in our study.

CONFLICTS OF INTEREST

All authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

SL, is the main author, has performed the analyses, and has done the main writing of the article and worked with interpretation of the results. GR, KH, NL, and KAW, contributed to the design, writing, and interpretation of the results. GEE, contributed to the analyses, design, writing, and interpretation of the results. KEE, contributed to the writing and interpretation of the results. All authors have revised the article for intellectual content and approved the final version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplemental Table 1 Results from simple linear regression analysis of PCS and MCS ten years after a *Giardia* -outbreak with respect to eight-categories exposure (IBSxCFxExposure status) after three, six and ten years, respectively

PCS	Estimated difference			P-value			N		
Exposure status	3 years	6 years	10 years	3 years	6 years	10 years	3 years	6 years	10 years
Neither condition among controls	55.5	55.1	55.4	ref	ref	ref	364	385	532
Neither condition among exposed	-0.2	0.1	-0.1	.78	.88	.84	163	226	280
IBS-only among controls	-2.9	-2.0	-4.4	.022	.097	<.001	41	46	75
IBS-only among exposed	-2.7	-3.8	-3.3	.004	<.001	<.001	85	99	146
CF-only among controls	-4.6	-4.3	-5.1	.007	.002	<.001	22	36	50
CF-only among exposed	-4.3	-7.7	-8.6	<.001	<.001	<.001	68	44	45
IBS and CF among controls	-8.5	-9.7	-7.5	<.001	<.001	<.001	20	12	18
IBS and CF among exposed	-8.3	-8.7	-13.1	<.001	<.001	<.001	142	97	101
						Total N	905	945	1247

MCS	Estimated difference			P-value			N		
Exposure status	3 years	6 years	10 years	3 years	6 years	10 years	3 years	6 years	10 years
Neither condition among controls	52.9	52.9	53.4	ref	ref	ref	368	390	536
Neither condition among exposed	-0.8	-1.3	-1.4	.35	.058	.023	164	226	282
IBS-only among controls	-2.6	0.8	-3.8	.067	.55	<.001	42	46	75
IBS-only among exposed	-2.2	-3.3	-3.6	.036	.001	<.001	85	99	146
CF-only among controls	-5.8	-5.0	-12.3	.002	.001	<.001	22	36	51
CF-only among exposed	-5.3	-5.8	-9.8	<.001	<.001	<.001	68	44	45
IBS and CF among controls	-4.6	-4.9	-10.1	.021	.049	<.001	20	12	19
IBS and CF among exposed	-7.9	-9.5	-11.5	<.001	<.001	<.001	142	97	101
						Total N	911	950	1255

PCS = Physical component summary (0-100); MCS = Mental component summary (0-100); IBS = Irritable bowel syndrome; CF = Chronic fatigue
Non-significant p-values are highlighted

Supplemental Table 2 Results from simple logistic regression analysis of dichotomous PCS and MCS ten years after a *Giardia*-outbreak with respect to eight-categories exposure (IBSxCFxExposure status) after three, six and ten years, respectively

PCS	OR for PCS below 45			P-value			N		
Exposure status	3 years	6 years	10 years	3 years	6 years	10 years	3 years	6 years	10 years
Neither condition among controls	ref	ref	ref	ref	ref	ref	364	385	532
Neither condition among exposed	1.3	1.0	1.0	.52	.97	.99	163	226	280
IBS-only among controls	2.4	2.0	4.4	.079	.13	<.001	41	46	75
IBS-only among exposed	1.9	2.6	2.4	.11	.003	.003	85	99	146
CF-only among controls	4.6	3.4	6.1	.006	.005	<.001	22	36	50
CF-only among exposed	4.7	8.8	14.0	<.001	<.001	<.001	68	44	45
IBS and CF among controls	10.5	12.9	6.9	<.001	<.001	<.001	20	12	18
IBS and CF among exposed	9.7	8.1	17.4	<.001	<.001	<.001	142	97	101
						Total N	905	945	1247

MCS	OR for MCS below 45			P-value			N		
Exposure status	3 years	6 years	10 years	3 years	6 years	10 years	3 years	6 years	10 years
Neither condition among controls	ref	ref	ref	ref	ref	ref	368	390	536
Neither condition among exposed	1.1	1.4	1.6	.74	.14	.030	164	226	282
IBS-only among controls	1.5	0.3	1.7	.38	.077	.091	42	46	75
IBS-only among exposed	2.3	2.0	2.1	.004	.015	.002	85	99	146
CF-only among controls	2.8	2.9	9.6	.036	.006	<.001	22	36	51
CF-only among exposed	3.9	4.2	7.6	<.001	<.001	<.001	68	44	45
IBS and CF among controls	2.3	1.9	15.9	.11	.36	<.001	20	12	19
IBS and CF among exposed	4.7	7.4	11.4	<.001	<.001	<.001	142	97	101
						Total N	911	950	1255

PCS = Physical component summary (0-100); MCS = Mental component summary (0-100); IBS = Irritable bowel syndrome; CF = Chronic fatigue
Non-significant p-values are highlighted

Supplemental Table 3 Results from simple linear regression analysis of PCS and MCS ten years after a *Giardia*-outbreak with IBS, CF and Exposure status as independent variables after three, six and ten years, respectively

		3 years	6 years	10 years
Regression model	**Outcome**	P-value for effect of status as exposed		
Exposure status, IBS, CF	PCS	.99	.37	.26
	MCS	.28	.002	.14
		P-value for interaction-term		
Exposure status, IBS, CF, Exposure statusxCF	PCS	.97	.42	<.001
	MCS	.57	.50	.027

PCS = Physical component summary (0-100); MCS = Mental component summary (0-100); IBS = Irritable bowel syndrome; CF = Chronic fatigue; Exposure status= Status as exposed or control

Non-significant p-values are highlighted

Supplemental Table 4 Means of the quality of life-subdomains of the short form 12 version 2 ten years after a *Giardia*-outbreak according to eight-categories exposure (IBSxCFxExposure status)

	Short form 12 version 2 subdomains							
Exposure status	**Physical functioning**	**Role physical**	**Bodily pain**	**General health**	**Vitality**	**Social functioning**	**Role emotional**	**Mental health**
Neither condition among controls	55.6	54.9	54.8	56.1	53.1	54.0	53.5	55.2
Neither condition among exposed	55.6	54.2	54.4	56.3	51.1	53.6	52.8	54.0
IBS-only among controls	52.5	51.5	49.4	50.4	48.5	50.1	50.2	51.2
IBS-only among exposed	54.0	50.5	50.7	51.4	48.6	50.0	50.5	52.0
CF-only among controls	50.6	47.4	49.1	47.6	38.4	46.9	43.4	44.9
CF-only among exposed	48.9	44.2	50.2	44.2	38.1	44.4	45.0	48.2
IBS and CF among controls	50.5	46.2	45.7	45.8	40.9	43.1	44.2	47.3
IBS and CF among exposed	46.1	40.5	42.8	39.7	37.3	39.7	43.3	45.2

CF = Chronic fatigue; IBS = Irritable bowel syndrome: Exposure status= Status as exposed or control

APPENDICES 1-4

APPENDIX 1

Errors in papers 1 and 2

Errors in papers 1 and 2

The following errors were found in paper 1 after publication:

1. In the abstract under "methods" we state that we have used "bivariate" and "multivariate" analyses, although the more correct terms are "univariable" and "multivariable".
2. Under "participants" on page two we state that four controls were excluded, when the correct number is five.
3. Under "statistical analyses" on page three we state that confounders evaluated were: "status as student or not in 2004, age, gender, work, income and level of education", where "income" should have been replaced by "marital status".
4. In paragraph four on page four we state that "vegetables" are significantly associated with exposure in the no-IBS stratum, but this is incorrect. The information is correctly displayed in Table 4.
5. There is an error in the "d" footnote in Table 2, where the text "is reasonably high, however" has been inserted between "Bresl" and "ow-Day". This is a post-proof error. Despite our repeated requests for amendment, the publisher has not responded.

The following error was found in paper 2 after publication:

1. On page 1071, paragraph three, we state that "...it nevertheless seems clear that postinfectious CI is a condition..." where "CI" should have been replaced with "CF".

APPENDIX 2

Questionnaires for three-year follow-up:
Exposed
Controls

Institutt for samfunnsmedisinske fag og Institutt for indremedisin
Universitetet i Bergen
Kalfarveien 31, 5018 BERGEN, Tlf: 55 58 61 00

Svarskjema – Studie etter giardia-epidemien

Regnr: ……..

1. Sivilstand:
☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har påbegynt?
☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?
☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. Var du student høsten 2004?
☐ Nei ☐ Ja, fulltid ☐ Ja, deltid

5. For kvinner: Er du gravid nå?
☐ Nei ☐ Ja ☐ Usikker

Søvn

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner, i motsetning til kun å føle deg trett? Spørsmålene gjelder din vanlige måte å reagere på i den senere tid. Selv om du ikke har gjort noe av dette i den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg. Sett ett kryss på hver linje.

Situasjon	Ville aldri døse/sovne	En liten sjanse for å døse/sovne	Moderat sjanse for å døse/sovne	Stor sjanse for å døse/sovne
6. Sitte og lese	☐	☐	☐	☐
7. Se på TV	☐	☐	☐	☐
8. Sitte, inaktiv på et offentlig sted (for eksempel teater eller et møte)	☐	☐	☐	☐
9. Som passasjer på en en-times biltur uten pause	☐	☐	☐	☐
10. Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
11. Sitte og snakke med noen	☐	☐	☐	☐
12. Sitte stille etter lunsj (uten å ha inntatt alkohol)	☐	☐	☐	☐
13. I en bil, som har stoppet for noen få minutter i trafikken	☐	☐	☐	☐

14. Hvor mye søvn trenger du for å være opplagt? …….. timer

15. I løpet av siste måned, hvor ofte har du vært plaget av søvnløshet?
☐ Aldri eller sjelden ☐ 1-2 ganger i måneden ☐ Omtrent en gang i uken ☐ Mer enn en gang i uken

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden. Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

16. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

17. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

27. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn én måned
☐ Fra én måned inntil seks måneder
☐ Fra seks måneder inntil ett år
☐ Fra ett år inntil tre år
☐ Tre år eller mer (før oktober 2004)

28. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden
☐ 50 % av tiden
☐ 75 % av tiden
☐ Hele tiden

Astma og allergi

29. Har du eller har du hatt astma? ☐ Nei ☐ Ja ☐ Usikker

30. Hvis ja, er dette bekreftet av lege? ☐ Nei ☐ Ja

31. Har du brukt astma-medisiner siste måned?
(spray, pulver/væske til inhalasjon, tabletter) ☐ Nei ☐ Ja

32. Har du eller har du hatt høysnue eller neseallergi? ☐ Nei ☐ Ja ☐ Usikker

Mageplager siste tre måneder

33. I løpet av de siste 3 måneder, hvor ofte har du følt deg ubehagelig mett etter et vanlig stort måltid?
- ☐ Aldri → Gå til spørsmål 35
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

34. Har du hatt denne ubehagelige metthets-følelsen etter måltid i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

35. I løpet av de siste 3 måneder, hvor ofte har du ikke kunnet fullføre et vanlig stort måltid?
- ☐ Aldri → Gå til spørsmål 37
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

36. Har du hatt dette problemet med ikke å kunne fullføre et vanlig stort måltid i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

37. I løpet av de siste 3 måneder, hvor ofte har du hatt smerter eller brenning midt i magen, over navlen, men ikke i brystet?
- ☐ Aldri → Gå til spørsmål 46 (på neste side)
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

38. Har du hatt denne smerten eller brenningen i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

39. Kom og forsvant denne smerten eller brenningen fullstendig i løpet av samme dag?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

40. Hvor alvorlig var vanligvis smerten eller brenningen i midten av magen, over navlen?
- ☐ Svært mild
- ☐ Mild
- ☐ Moderat
- ☐ Sterk
- ☐ Svært sterk

41. Ble denne smerten eller brenningen påvirket av spising?
- ☐ Ikke påvirket av spising
- ☐ Mer smerter etter spising
- ☐ Mindre smerter etter spising

42. Ble denne smerten eller brenningen lindret av å ta syrenøytraliserende midler?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

43. Ble denne smerten eller brenningen vanligvis bedre eller forsvant den etter at du hadde hatt avføring eller luftavgang fra endetarmen?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

44. Når denne smerten eller brenningen begynte, hadde du vanligvis endring i antall avføringer (enten hyppigere eller sjeldnere avføring)?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

45. Når denne smerten eller brenningen begynte, hadde du vanligvis løsere eller hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

46. Har lege diagnostisert sykdom i spiserør eller magesekk hos deg siste 3 år?
- ☐ Nei
- ☐ Ja

Hvis ja, hva slags sykdom:

……

47. I løpet av siste 3 måneder, hvor ofte har du hatt plagsom kvalme?
- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

48. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?
- ☐ Aldri → Gå til spørsmål 58
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

49. Har du hatt kun smerter (ikke ubehag eller en blanding av ubehag og smerter)?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

50. For kvinner: Har du kun hatt dette ubehaget eller smerten i forbindelse med menstruasjonsblødning og ikke til andre tider?
- ☐ Nei
- ☐ Ja
- ☐ Ikke aktuelt fordi jeg ikke har menstruasjon

51. Når du hadde denne smerten, hvor ofte hemmet eller begrenset den daglige gjøremål (for eksempel arbeid, gjøremål i hjemmet eller sosiale aktiviteter?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

52. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

53. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

54. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

55. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

56. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

57. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

58. I løpet av de siste 3 måneder, hvor ofte har du hatt færre enn tre (0-2) avføringer hver uke?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

59. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

60. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

61. I løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

62. I løpet av de siste 3 måneder, hvor ofte har du vært oppblåst eller utspilt i magen?

- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

63. I løpet av de siste 3 måneder, hvor ofte har du hatt så dårlig lukt av avføring eller luft fra endetarmen at det påvirket daglige gjøremål (f.eks. unngått å være med andre, bruke andres toalett)?

- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

64. I løpet av siste 3 måneder, hvor ofte har du hatt vedvarende smerter i midten eller på høyre side øverst i magen?

- ☐ Aldri → Gå til spørsmål 69
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

65. Varte denne smerten 30 minutter eller lenger?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

66. Bygget denne smerten seg opp til en vedvarende, sterk smerte?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

67. Forsvant denne smerten fullstendig mellom hver gang den kom?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

68. Hindret denne smerten deg i vanlige aktiviteter, eller førte den til at du øyeblikkelig oppsøkte lege eller legevakt?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

69. Dersom du drikker melk, får du da plager fra magen?

- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

70. Dersom du får plager når du drikker melk, om lag når begynte plagene?

År: …….. Måned: …… ☐ Husker ikke

71. Reagerer du med plager fra magen dersom du inntar spesiell mat eller drikke?

- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

72. Dersom du reagerer, hva slags mat eller drikke reagerer du på:

……

……

73. Har du mageplager NÅ som du ikke hadde før du fikk Giardia-infeksjon?
☐ Nei ☐ Ja ☐ Usikker

Hvis **ja**, prøv å gradere dine symptomer den siste måneden i tabellen under:
Angi på en skala fra 1 til 10: 0 = ingen symptomer og 10 = alvorlige symptomer

Spørsmål	**Svar**
74. Kvalme	
75. Oppblåsthet	
76. Magesmerter	
77. Forstoppelse	
78. Diaré	
79. Nedsatt appetitt	

Informasjon og behandling

Synes du at du fikk tilstrekkelig **informasjon** etter at du ble syk med giardia-infeksjon?
(svar "Ikke aktuelt" for instanser du ikke var i kontakt med)

	I svært liten grad	I liten grad	I noen grad	I stor grad	I svært stor grad	Ikke aktuelt
80. Fra fastlege	☐	☐	☐	☐	☐	☐
81. Fra Bergen legevakt						
82. Fra sykehus	☐	☐	☐	☐	☐	☐
83. Fra Bergen kommune (nettsider, løpesedler i posten, informasjon gjennom avisem.v.)						

Synes du at du fikk tilfredsstillende **behandling** etter at du ble syk med giardia-infeksjon?
(svar "Ikke aktuelt" for instanser du ikke var i kontakt med)

	I svært liten grad	I liten grad	I noen grad	I stor grad	I svært stor grad	Ikke aktuelt
84. Hos fastlege	☐	☐	☐	☐	☐	☐
85. Ved Bergen legevakt						
86. På sykehus	☐	☐	☐	☐	☐	☐

Jeg samtykker i at opplysingene ovenfor kan kobles med opplysninger om meg i offentlige helseregistre for forskningsformål (sett kryss): ☐

Jeg samtykker i at tidligere innhentede data om meg (avføringsprøver, blodprøver etc) i forbindelse med giardia-sykdom kan brukes i dette og senere forskningsprosjekter om giardia (sett kryss): ☐

Takk for hjelpen!

Institutt for samfunnsmedisinske fag og Institutt for indremedisin
Universitetet i Bergen
Kalfarveien 31, 5018 BERGEN, Tlf: 55 58 61 00

Svarskjema – Studie etter giardia-epidemien

Regnr: ……..

Mener du at du har hatt giardia-infeksjon?

☐ Nei ☐ Ja ☐ Usikker

Hvis **ja**: Når fikk du giardia-infeksjonen? Måned: ……... År: …….

Hvis **ja**: Ble giardia-infeksjon bekreftet av lege? ☐ Ja ☐ Nei ☐ Usikker

1. Sivilstand:
☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har påbegynt?
☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?
☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. Var du student høsten 2004?
☐ Nei ☐ Ja, fulltid ☐ Ja, deltid

5. For kvinner: Er du gravid nå?
☐ Nei ☐ Ja ☐ Usikker

Søvn

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner, i motsetning til kun å føle deg trett? Spørsmålene gjelder din vanlige måte å reagere på i den senere tid. Selv om du ikke har gjort noe av dette i den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg. Sett ett kryss på hver linje.

Situasjon	Ville aldri døse/sovne	En liten sjanse for å døse/sovne	Moderat sjanse for å døse/sovne	Stor sjanse for å døse/sovne
6. Sitte og lese	☐	☐	☐	☐
7. Se på TV	☐	☐	☐	☐
8. Sitte, inaktiv på et offentlig sted (for eksempel teater eller et møte)	☐	☐	☐	☐
9. Som passasjer på en en-times biltur uten pause	☐	☐	☐	☐
10. Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
11. Sitte og snakke med noen	☐	☐	☐	☐
12. Sitte stille etter lunsj (uten å ha inntatt alkohol)	☐	☐	☐	☐
13. I en bil, som har stoppet for noen få minutter i trafikken	☐	☐	☐	☐

14. Hvor mye søvn trenger du for å være opplagt? …….. timer

15. I løpet av siste måned, hvor ofte har du vært plaget av søvnløshet?
☐ Aldri eller sjelden ☐ 1-2 ganger i måneden ☐ Omtrent en gang i uken ☐ Mer enn en gang i uken

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden. Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

16. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

17. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

27. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn én måned
☐ Fra én måned inntil seks måneder
☐ Fra seks måneder inntil ett år
☐ Fra ett år inntil tre år
☐ Tre år eller mer (før oktober 2004)

28. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden
☐ 50 % av tiden
☐ 75 % av tiden
☐ Hele tiden

Astma og allergi

29. Har du eller har du hatt astma? ☐ Nei ☐ Ja ☐ Usikker

30. Hvis ja, er dette bekreftet av lege? ☐ Nei ☐ Ja

31. Har du brukt astma-medisiner siste måned?
(spray, pulver/væske til inhalasjon, tabletter) ☐ Nei ☐ Ja

32. Har du eller har du hatt høysnue eller neseallergi? ☐ Nei ☐ Ja ☐ Usikker

Mageplager siste tre måneder

33. I løpet av de siste 3 måneder, hvor ofte har du følt deg ubehagelig mett etter et vanlig stort måltid?
- ☐ Aldri → Gå til spørsmål 35
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

34. Har du hatt denne ubehagelige metthets-følelsen etter måltid i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

35. I løpet av de siste 3 måneder, hvor ofte har du ikke kunnet fullføre et vanlig stort måltid?
- ☐ Aldri → Gå til spørsmål 37
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

36. Har du hatt dette problemet med ikke å kunne fullføre et vanlig stort måltid i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

37. I løpet av de siste 3 måneder, hvor ofte har du hatt smerter eller brenning midt i magen, over navlen, men ikke i brystet?
- ☐ Aldri → Gå til spørsmål 46 (på neste side)
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

38. Har du hatt denne smerten eller brenningen i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

39. Kom og forsvant denne smerten eller brenningen fullstendig i løpet av samme dag?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

40. Hvor alvorlig var vanligvis smerten eller brenningen i midten av magen, over navlen?
- ☐ Svært mild
- ☐ Mild
- ☐ Moderat
- ☐ Sterk
- ☐ Svært sterk

41. Ble denne smerten eller brenningen påvirket av spising?
- ☐ Ikke påvirket av spising
- ☐ Mer smerter etter spising
- ☐ Mindre smerter etter spising

42. Ble denne smerten eller brenningen lindret av å ta syrenøytraliserende midler?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

43. Ble denne smerten eller brenningen vanligvis bedre eller forsvant den etter at du hadde hatt avføring eller luftavgang fra endetarmen?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

44. Når denne smerten eller brenningen begynte, hadde du vanligvis endring i antall avføringer (enten hyppigere eller sjeldnere avføring)?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

45. Når denne smerten eller brenningen begynte, hadde du vanligvis løsere eller hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

46. Har lege diagnostisert sykdom i spiserør eller magesekk hos deg siste 3 år?
- ☐ Nei
- ☐ Ja

Hvis ja, hva slags sykdom:

……

47. I løpet av siste 3 måneder, hvor ofte har du hatt plagsom kvalme?
- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

48. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?
- ☐ Aldri → Gå til spørsmål 58
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

49. Har du hatt kun smerter (ikke ubehag eller en blanding av ubehag og smerter)?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

50. For kvinner: Har du kun hatt dette ubehaget eller smerten i forbindelse med menstruasjonsblødning og ikke til andre tider?
- ☐ Nei
- ☐ Ja
- ☐ Ikke aktuelt fordi jeg ikke har menstruasjon

51. Når du hadde denne smerten, hvor ofte hemmet eller begrenset den daglige gjøremål (for eksempel arbeid, gjøremål i hjemmet eller sosiale aktiviteter?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

52. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

53. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

54. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

55. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

56. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

57. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

58. I løpet av de siste 3 måneder, hvor ofte har du hatt færre enn tre (0-2) avføringer hver uke?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

59. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

60. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

61. I løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

62. I løpet av de siste 3 måneder, hvor ofte har du vært oppblåst eller utspilt i magen?

- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

63. I løpet av de siste 3 måneder, hvor ofte har du hatt så dårlig lukt av avføring eller luft fra endetarmen at det påvirket daglige gjøremål (f.eks. unngått å være med andre, bruke andres toalett)?

- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

64. I løpet av siste 3 måneder, hvor ofte har du hatt vedvarende smerter i midten eller på høyre side øverst i magen?

- ☐ Aldri → Gå til spørsmål 69
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

65. Varte denne smerten 30 minutter eller lenger?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

66. Bygget denne smerten seg opp til en vedvarende, sterk smerte?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

67. Forsvant denne smerten fullstendig mellom hver gang den kom?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

68. Hindret denne smerten deg i vanlige aktiviteter, eller førte den til at du øyeblikkelig oppsøkte lege eller legevakt?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

69. Dersom du drikker melk, får du da plager fra magen?

- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

70. Dersom du får plager når du drikker melk, om lag når begynte plagene?

År: …….. Måned: …… ☐ Husker ikke

71. Reagerer du med plager fra magen dersom du inntar spesiell mat eller drikke?

- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

72. Dersom du reagerer, hva slags mat eller drikke reagerer du på:

……

……

Jeg samtykker i at opplysingene ovenfor kan kobles med opplysninger om meg i offentlige helseregistre for forskningsformål (sett kryss): ☐

Takk for hjelpen!

APPENDIX 3

Questionnaires for six-year follow-up:
Exposed
Controls

41. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?
- ☐ Aldri → Gå til spørsmål 50
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

42. For kvinner: Har du kunn hatt dette ubehaget eller smerten i forbindelse med menstruasjons-blødning og ikke til andre tider?
- ☐ Nei
- ☐ Ja
- ☐ Ikke aktuelt fordi jeg ikke har menstruasjon

43. Når du hadde denne smerten, hvor ofte hemmet eller begrenset de det daglige gjøremål (for eksempel arbeid, gjøremål i hjemmet eller sosiale aktiviteter?)
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

44. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

45. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

46. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

47. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid
- ☐ Det meste av tiden
- ☐ Alltid

48. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

49. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

50. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?
- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

51. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

52. I løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?
- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

53. I løpet av de siste 3 måneder, hvor ofte har du vært oppblåst eller utspilt i magen?
- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

54. Dersom du drikker melk, får du da plager fra magen?
- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

Jeg samtykker i at opplysingene ovenfor kan kobles med opplysninger om meg i offentlige registre (som helse/trygderegistre) og sosioøkonomiske data i Statistisk sentralbyrå, for forskningsformål (sett kryss): ☐

Takk for hjelpen!

HELSE BERGEN
Haukeland Universitetssykehus
5021 Bergen

Regnr: ……..

Svarskjema – Studie 6 år etter *Giardia*-epidemien

1. Sivilstand:
☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har påbegynt?
☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?
☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. For kvinner: Er du gravid nå?
☐ Nei ☐ Ja ☐ Usikker

Søvn

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner, i motsetning til kun å føle deg trett? Spørsmålene gjelder din vanlige måte å reagere på i den senere tid. Selv om du ikke har gjort noe av dette i den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg. Sett ett kryss på hver linje.

Situasjon	Ville aldri døse/sovne	En liten sjanse for å døse/sovne	Moderat sjanse for å døse/sovne	Stor sjanse for å døse/sovne
5. Sitte og lese	☐	☐	☐	☐
6. Se på TV	☐	☐	☐	☐
7. Sitte, inaktiv på et offentlig sted (for eksempel teater eller et møte)	☐	☐	☐	☐
8. Som passasjer på en en-times biltur uten pause	☐	☐	☐	☐
9. Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
10. Sitte og snakke med noen	☐	☐	☐	☐
11. Sitte stille etter lunsj (uten å ha inntatt alkohol)	☐	☐	☐	☐
12. I en bil, som har stoppet for noen få minutter i trafikken	☐	☐	☐	☐

13. Hvor mye søvn trenger du for å være opplagt? …….. timer

14. I løpet av siste måned, hvor ofte har du vært plaget av søvnløshet?
☐ Aldri eller sjelden ☐ 1-2 ganger i måneden ☐ Omtrent en gang i uken ☐ Mer enn en gang i uken

Skjema 202902 - Bording AS

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd **den siste måneden.** Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

16. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

17. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

27. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn en måned
☐ Mellom en og seks måneder
☐ Seks måneder eller mer

28. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden ☐ 75 % av tiden
☐ 50 % av tiden ☐ Hele tiden

Astma og allergi

29. Har du eller har du hatt astma? ☐ Nei ☐ Ja ☐ Usikker

30. Hvis ja, er dette bekreftet av lege? ☐ Nei ☐ Ja

31. Har du brukt astma-medisiner siste måned? (spray, pulver/væske til inhalasjon, tabletter) ☐ Nei ☐ Ja

32. Har du eller har du hatt høysnue eller neseallergi? ☐ Nei ☐ Ja ☐ Usikker

32b. Får du utslett av metallknapper, metallspenner, smykker (f.eks ørepynt) eller andre metallgjenstander som er i kontakt med huden? (bortsett fra under ringer på fingrene) ☐ Nei ☐ Ja ☐ Usikker

Urinveissymptomer siste fire uker

I de følgende spørsmålene ber vi deg tenke på dine blæresymptomer alt i alt i de siste 4 ukene. Vennligst svar på hvert spørsmål om hvor ofte du har følt det slik, så godt du kan.

U1. Tar det tid før du begynner å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U2. Er du nødt til å anstrenge deg for å fortsette vannlatingen?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U3. Hvor mange ganger i løpet av dagen har du vanligvis vannlating?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U4. Hvor ofte står du vanligvis opp om natten for å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U5. Er du nødt til å skynde deg på toalettet for å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U6. Lekker det urin før du når frem til toalettet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

Mageplager siste tre måneder

33. I løpet av de siste 3 måneder, hvor ofte har du følt deg ubehagelig mett etter et vanlig stort måltid?
☐ Aldri → Gå til spørsmål 35
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

34. Har du hatt denne ubehagelige metthets-følelsen etter måltid i 6 måneder eller lenger?
☐ Nei
☐ Ja

35. I løpet av de siste 3 måneder, hvor ofte har du ikke kunnet fullføre et vanlig stort måltid?
☐ Aldri → Gå til spørsmål 37
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

36. Har du hatt dette problemet med ikke å kunne fullføre et vanlig stort måltid i 6 måneder eller lenger?
☐ Nei
☐ Ja

37. I løpet av de siste 3 måneder, hvor ofte har du hatt smerter eller brenning midt i magen, over navlen, men ikke i brystet?
☐ Aldri → Gå til spørsmål 46 (på neste side)
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

38. Har du hatt denne smerten eller brenningen i 6 måneder eller lenger?
☐ Nei
☐ Ja

39. Har lege diagnostisert sykdom i spiserør eller magesekk hos deg siste 3 år?
☐ Nei
☐ Ja

Hvis ja, hva slags sykdom:
.....

40. I løpet av siste 3 måneder, hvor ofte har du hatt plagsom kvalme?
☐ Aldri
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

41. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?
- ☐ Aldri → Gå til spørsmål 50
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

42. For kvinner: Har du kunn hatt dette ubehaget eller smerten i forbindelse med menstruasjons-blødning og ikke til andre tider?
- ☐ Nei
- ☐ Ja
- ☐ Ikke aktuelt fordi jeg ikke har menstruasjon

43. Når du hadde denne smerten, hvor ofte hemmet eller begrenset de det daglige gjøremål (for eksempel arbeid, gjøremål i hjemmet eller sosiale aktiviteter?)
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

44. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?
- ☐ Nei
- ☐ Ja

45. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

46. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

47. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid
- ☐ Det meste av tiden
- ☐ Alltid

48. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

49. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

50. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?
- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

51. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?
- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

52. I løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?
- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

53. I løpet av de siste 3 måneder, hvor ofte har du vært oppblåst eller utspilt i magen?
- ☐ Aldri
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

54. Dersom du drikker melk, får du da plager fra magen?
- ☐ Nei, ingen plager
- ☐ Lette plager
- ☐ Middels store plager
- ☐ Store plager

Jeg samtykker i at opplysingene ovenfor kan kobles med opplysninger om meg i offentlige registre (som helse/trygderegistre) og sosioøkonomiske data i Statistisk sentralbyrå, for forskningsformål (sett kryss): ☐

Takk for hjelpen!

HELSE BERGEN
Haukeland Universitetssykehus
5021 Bergen

Regnr: .....

Svarskjema – Studie 6 år etter *Giardia*-epidemien

Mener du at du har hatt *Giardia* infeksjon noen gang?
☐ Nei ☐ Ja ☐ Usikker

Hvis ja: Når fikk du *Giardia* infeksjonen? **Måned:** ..... **År:** .....

Hvis ja: Ble *Giardia* infeksjonen bekreftet av lage?
☐ Nei ☐ Ja ☐ Usikker

1. Sivilstand:
☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har påbegynt?
☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?
☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. For kvinner: Er du gravid nå?
☐ Nei ☐ Ja ☐ Usikker

Søvn

Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner, i motsetning til kun å føle deg trett? Spørsmålene gjelder din vanlige måte å reagere på i den senere tid. Selv om du ikke har gjort noe av dette i den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg. Sett ett kryss på hver linje.

Situasjon	Ville aldri døse/sovne	En liten sjanse for å døse/sovne	Moderat sjanse for å døse/sovne	Stor sjanse for å døse/sovne
5. Sitte og lese	☐	☐	☐	☐
6. Se på TV	☐	☐	☐	☐
7. Sitte, inaktiv på et offentlig sted (for eksempel teater eller et møte)	☐	☐	☐	☐
8. Som passasjer på en en-times biltur uten pause	☐	☐	☐	☐
9. Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
10. Sitte og snakke med noen	☐	☐	☐	☐
11. Sitte stille etter lunsj (uten å ha inntatt alkohol)	☐	☐	☐	☐
12. I en bil, som har stoppet for noen få minutter i trafikken	☐	☐	☐	☐

13. Hvor mye søvn trenger du for å være opplagt? ..... timer

14. I løpet av siste måned, hvor ofte har du vært plaget av søvnløshet?
☐ Aldri eller sjelden ☐ 1-2 ganger i måneden ☐ Omtrent en gang i uken ☐ Mer enn en gang i uken

Skjema 202901 - Boxding AS

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd **den siste måneden.** Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

16. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

17. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

27. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn en måned
☐ Mellom en og seks måneder
☐ Seks måneder eller mer

28. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden ☐ 75 % av tiden
☐ 50 % av tiden ☐ Hele tiden

Astma og allergi

29. Har du eller har du hatt astma? ☐ Nei ☐ Ja ☐ Usikker

30. Hvis ja, er dette bekreftet av lege? ☐ Nei ☐ Ja

31. Har du brukt astma-medisiner siste måned? (spray, pulver/væske til inhalasjon, tabletter) ☐ Nei ☐ Ja

32. Har du eller har du hatt høysnue eller neseallergi? ☐ Nei ☐ Ja ☐ Usikker

32b. Får du utslett av metallknapper, metallspenner, smykker (f.eks ørepynt) eller andre metallgjenstander som er i kontakt med huden? (bortsett fra under ringer på fingrene) ☐ Nei ☐ Ja ☐ Usikker

Urinveissymptomer siste fire uker

I de følgende spørsmålene ber vi deg tenke på dine blæresymptomer alt i alt i de siste 4 ukene. Vennligst svar på hvert spørsmål om hvor ofte du har følt det slik, så godt du kan.

U1. Tar det tid før du begynner å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U2. Er du nødt til å anstrenge deg for å fortsette vannlatingen?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U3. Hvor mange ganger i løpet av dagen har du vanligvis vannlating?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U4. Hvor ofte står du vanligvis opp om natten for å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U5. Er du nødt til å skynde deg på toalettet for å late vannet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

U6. Lekker det urin før du når frem til toalettet?
☐ Aldri ☐ Som oftest
☐ Sjelden ☐ Alltid
☐ Av og til

Mageplager siste tre måneder

33. I løpet av de siste 3 måneder, hvor ofte har du følt deg ubehagelig mett etter et vanlig stort måltid?
☐ Aldri → Gå til spørsmål 35
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

34. Har du hatt denne ubehagelige metthets-følelsen etter måltid i 6 måneder eller lenger?
☐ Nei
☐ Ja

35. I løpet av de siste 3 måneder, hvor ofte har du ikke kunnet fullføre et vanlig stort måltid?
☐ Aldri → Gå til spørsmål 37
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

36. Har du hatt dette problemet med ikke å kunne fullføre et vanlig stort måltid i 6 måneder eller lenger?
☐ Nei
☐ Ja

37. I løpet av de siste 3 måneder, hvor ofte har du hatt smerter eller brenning midt i magen, over navlen, men ikke i brystet?
☐ Aldri → Gå til spørsmål 46 (på neste side)
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

38. Har du hatt denne smerten eller brenningen i 6 måneder eller lenger?
☐ Nei
☐ Ja

39. Har lege diagnostisert sykdom i spiserør eller magesekk hos deg siste 3 år?
☐ Nei
☐ Ja

Hvis ja, hva slags sykdom:
.....

40. I løpet av siste 3 måneder, hvor ofte har du hatt plagsom kvalme?
☐ Aldri
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

APPENDIX 4

Questionnaires for ten-year follow-up:
Exposed
Controls

Mageplager siste tre måneder

34. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?

- ☐ Aldri → Gå til spørsmål 43
- ☐ Mindre enn 1 dag i måneden
- ☐ En dag i måneden
- ☐ 2-3 dager i måneden
- ☐ En dag i uka
- ☐ Mer enn en dag i uka
- ☐ Hver dag

35. For kvinner: Har du kun hatt dette ubehaget eller smerten i forbindelse med menstruasjons-blødning og ikke til andre tider?

- ☐ Nei ☐ Ja
- ☐ Ikke aktuelt fordi jeg ikke har menstruasjon

36. Når du hadde denne smerten, hvor ofte hemmet eller begrenset den daglige gjøremål?
(f.eks. arbeid, gjøremål hjemme eller sosiale aktiviteter)

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

37. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?

- ☐ Nei ☐ Ja

38. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

39. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

40. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

41. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

42. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

43. I løpet av de siste 3 måneder, hvor ofte har du hatt færre enn tre (0-2) avføringer hver uke?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

44. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

45. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?

- ☐ Sjelden/aldri
- ☐ Noen ganger
- ☐ Ofte
- ☐ Det meste av tiden
- ☐ Alltid

46. løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?

- ☐ Sjelden/aldri
- ☐ Ca. 25% av tiden
- ☐ Ca. 50% av tiden
- ☐ Ca. 75% av tiden
- ☐ Alltid, 100% av tiden

Jeg samtykker i at opplysningene ovenfor kan kobles for forskningsformål med opplysninger om meg i offentlige helse-/trygderegistre og med sosioøkonomiske data i Statistisk sentralbyrå (sett kryss): ☐

Takk for hjelpen!

uni Research

Allmennmedisinsk forskningsenhet
Uni Health, Research Unit for General Practice in Bergen
besøksadresse Kalfarveien 31, Bergen
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web uni.no/helse/afe **epost** afe@uni.no
organisasjonanummer 985 827 117 mva

Reg.nr: .....

Svarskjema – Studie 10 år etter *Giardia*-epidemien

1. Sivilstand:

☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har fullført?

☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?

☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. For kvinner: Er du gravid nå?

☐ Nei ☐ Ja ☐ Usikker

Spørsmål om helse og trivsel

Denne delen handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å gjennomføre dine daglige gjøremål. For hvert av de følgende spørsmålene sett et X i den ene luken som best beskriver ditt svar.

5. Stort sett vil du si at din helse er:

☐ Utmerket ☐ Meget god ☐ God ☐ Nokså god ☐ Dårlig

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag.
Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene **nå**? Hvis ja, hvor mye?

6. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid

☐ Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt

7. Gå opp trappen flere etasjer

☐ Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt

I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av din fysiske helse**?

8. Du har utrettet mindre enn du hadde ønsket

☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

9. Du har vært hindret i å utføre visse typer arbeid eller gjøremål

☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

Skjema 202902 - BordingCognito AS

I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av følelsesmessige problemer** (som for eksempel å være deprimert eller engstelig)?

10. Du har utrettet mindre enn du hadde ønsket
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

11. Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

12. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?
☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

Disse spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det **de siste 4 ukene**.
For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.
Hvor ofte i løpet av **de siste 4 ukene** har du:

	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
13. Følt det rolig og harmonisk	☐	☐	☐	☐	☐
14. Hatt mye overskudd	☐	☐	☐	☐	☐
15. Følt deg nedfor og deprimert	☐	☐	☐	☐	☐

16. I løpet av de siste 4 ukene, hvor ofte har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger, osv.)?
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd **den siste måneden.** Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

17. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

27. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

28. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn en måned
☐ Mellom en og seks måneder
☐ Seks måneder eller mer

29. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden ☐ 75 % av tiden
☐ 50 % av tiden ☐ Hele tiden

Smerter i kroppen

30. Bruk følgende skala for å angi alvorlighetsgrad for hvert problem i løpet av siste uke. Sett kryss i riktig boks.

0: Ikke noe problem.
1: Lett eller middels problematisk; stort sett milde som kan komme og gå
2: Moderat; betydelig problem; ofte tilstedeværende og/eller på et moderat nivå
3: Alvorlig: Kontinuerlige, problemene forstyrrer livsutfoldelsen i stor grad

Utmattelse	☐ 0	☐ 1	☐ 2	☐ 3
Problemer med å tenke og huske	☐ 0	☐ 1	☐ 2	☐ 3
Våkner opp trett (ikke uthvilt)	☐ 0	☐ 1	☐ 2	☐ 3

31. Har du vært plaget med noen av de følgende symptomene i løpet av de siste 6 månedene?

Smerte/krampe nedre del av magen	☐ Ja	☐ Nei
Depresjon	☐ Ja	☐ Nei
Hodepine	☐ Ja	☐ Nei

32. Vennligst angi om du har hatt smerte eller ømhet på hvert område som er listet opp nedenfor i løpet av de siste 7 dager. Sett et kryss i boksen hvor du har hatt smerte eller ømhet. Sørg for å markere høyre side og venstre side hver for seg.

☐ Skulder, venstre ☐ Skulder, høyre	☐ Lår / kne, venstre ☐ Lår / kne, høyre	☐ Korsrygg ☐ Øvre del av ryggen
☐ Hofte, venstre ☐ Hofte, høyre	☐ Legg / fot, venstre ☐ Legg / fot, høyre	☐ Nakke/ hals
☐ Overarm, venstre ☐ Overarm, høyre	☐ Kjeve, venstre ☐ Kjeve, høyre	☐ Ingen smerte i noen av disse områdene
☐ Underarm, venstre ☐ Underarm, høyre	☐ Brystkasse ☐ Buk/ Mage	

33. Alt i alt, har symptomene nevnt over i del 30-32 vært tilstede i minst 3 måneder? ☐ Ja ☐ Nei

Mageplager siste tre måneder

34. I løpet av siste tre måneder, hvor ofte har du hatt ubehag eller smerter noe sted i magen?

☐ Aldri → Gå til spørsmål 43
☐ Mindre enn 1 dag i måneden
☐ En dag i måneden
☐ 2-3 dager i måneden
☐ En dag i uka
☐ Mer enn en dag i uka
☐ Hver dag

35. For kvinner: Har du kun hatt dette ubehaget eller smerten i forbindelse med menstruasjons-blødning og ikke til andre tider?

☐ Nei ☐ Ja
☐ Ikke aktuelt fordi jeg ikke har menstruasjon

36. Når du hadde denne smerten, hvor ofte hemmet eller begrenset den daglige gjøremål?
(f.eks. arbeid, gjøremål hjemme eller sosiale aktiviteter)

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

37. Har du hatt dette ubehaget eller smerten i 6 måneder eller lenger?

☐ Nei ☐ Ja

38. Hvor ofte ble ubehaget eller smerten i magen bedre eller forsvant etter at du hadde hatt avføring?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

39. Når dette ubehaget eller smerten begynte, hadde du hyppigere avføring?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

40. Når dette ubehaget eller smerten begynte, hadde du sjeldnere avføring?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

41. Når dette ubehaget eller smerten begynte, hadde du løsere avføring?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

42. Når dette ubehaget eller smerten begynte, hvor ofte hadde du hardere avføring?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

43. I løpet av de siste 3 måneder, hvor ofte har du hatt færre enn tre (0-2) avføringer hver uke?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

44. I løpet av siste tre måneder, hvor ofte har du hatt hard eller klumpete avføring?

☐ Sjelden/aldri
☐ Ca. 25% av tiden
☐ Ca. 50% av tiden
☐ Ca. 75% av tiden
☐ Alltid, 100% av tiden

45. I løpet av de siste 3 måneder, hvor ofte har du hatt 4 eller flere avføringer i løpet av en dag?

☐ Sjelden/aldri
☐ Noen ganger
☐ Ofte
☐ Det meste av tiden
☐ Alltid

46. løpet av de siste 3 måneder, hvor ofte har du hatt løs, grøtete eller vandig avføring?

☐ Sjelden/aldri
☐ Ca. 25% av tiden
☐ Ca. 50% av tiden
☐ Ca. 75% av tiden
☐ Alltid, 100% av tiden

Jeg samtykker i at opplysningene ovenfor kan kobles for forskningsformål med opplysninger om meg i offentlige helse-/trygderegistre og med sosioøkonomiske data i Statistisk sentralbyrå (sett kryss): ☐

Takk for hjelpen!

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Reg.nr: .....

Svarskjema – Studie 10 år etter *Giardia*-epidemien

Mener du at du har hatt *Giardia* infeksjon noen gang?
☐ Nei ☐ Ja ☐ Usikker

Hvis ja: Når fikk du Giardia infeksjonen? Måned:..... År: .....

Hvis ja: Ble Giardia infeksjonen bekreftet av lege? ☐ Nei ☐ Ja ☐ Usikker

1. Sivilstand:
☐ Enslig ☐ Gift/samboer ☐ Skilt/separert ☐ Enke/enkemann

2. Hva er det høyeste utdanningsnivå du har fullført?
☐ Grunnskole ☐ Videregående skole ☐ Universitet eller høyskole

3. Hvilken hovedinntektskilde har du?
☐ Arbeidstaker ☐ Student/skoleelev/militær ☐ Alderspensjonist
☐ Selvstendig næringsdrivende ☐ Arbeidsledig ☐ Annet
☐ Hjemmeværende ☐ Uføretrygdet

4. For kvinner: Er du gravid nå?
☐ Nei ☐ Ja ☐ Usikker

Spørsmål om helse og trivsel

Denne delen handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å gjennomføre dine daglige gjøremål. For hvert av de følgende spørsmålene sett et X i den ene luken som best beskriver ditt svar.

5. Stort sett vil du si at din helse er:
☐ Utmerket ☐ Meget god ☐ God ☐ Nokså god ☐ Dårlig

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag.
Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene **nå**? Hvis ja, hvor mye?

6. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid
☐ Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt

7. Gå opp trappen flere etasjer
☐ Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt

I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av din fysiske helse**?

8. Du har utrettet mindre enn du hadde ønsket
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

9. Du har vært hindret i å utføre visse typer arbeid eller gjøremål
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

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I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål **på grunn av følelsesmessige problemer** (som for eksempel å være deprimert eller engstelig)?

10. Du har utrettet mindre enn du hadde ønsket
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

11. Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

12. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?
☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

Disse spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det **de siste 4 ukene**.
For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.
Hvor ofte i løpet av **de siste 4 ukene** har du:

	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
13. Følt det rolig og harmonisk	☐	☐	☐	☐	☐
14. Hatt mye overskudd	☐	☐	☐	☐	☐
15. Følt deg nedfor og deprimert	☐	☐	☐	☐	☐

16. I løpet av de siste 4 ukene, hvor ofte har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger, osv.)?
☐ Hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

Slitenhet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd **den siste måneden.** Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

17. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

18. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

19. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

20. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

21. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

22. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

24. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

25. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

26. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

27. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

28. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn en måned
☐ Mellom en og seks måneder
☐ Seks måneder eller mer

29. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden ☐ 75 % av tiden
☐ 50 % av tiden ☐ Hele tiden

Smerter i kroppen

30. Bruk følgende skala for å angi alvorlighetsgrad for hvert problem i løpet av siste uke. Sett kryss i riktig boks.

0: Ikke noe problem.
1: Lett eller middels problematisk; stort sett milde som kan komme og gå
2: Moderat; betydelig problem; ofte tilstedeværende og/eller på et moderat nivå
3: Alvorlig: Kontinuerlige, problemene forstyrrer livsutfoldelsen i stor grad

Utmattelse	☐ 0	☐ 1	☐ 2	☐ 3
Problemer med å tenke og huske	☐ 0	☐ 1	☐ 2	☐ 3
Våkner opp trett (ikke uthvilt)	☐ 0	☐ 1	☐ 2	☐ 3

31. Har du vært plaget med noen av de følgende symptomene i løpet av de siste 6 månedene?

Smerte/krampe nedre del av magen	☐ Ja	☐ Nei
Depresjon	☐ Ja	☐ Nei
Hodepine	☐ Ja	☐ Nei

32. Vennligst angi om du har hatt smerte eller ømhet på hvert område som er listet opp nedenfor i løpet av de siste 7 dager. Sett et kryss i boksen hvor du har hatt smerte eller ømhet. Sørg for å markere høyre side og venstre side hver for seg.

☐ Skulder, venstre ☐ Skulder, høyre	☐ Lår / kne, venstre ☐ Lår / kne, høyre	☐ Korsrygg ☐ Øvre del av ryggen
☐ Hofte, venstre ☐ Hofte, høyre	☐ Legg / fot, venstre ☐ Legg / fot, høyre	☐ Nakke/ hals
☐ Overarm, venstre ☐ Overarm, høyre	☐ Kjeve, venstre ☐ Kjeve, høyre	☐ Ingen smerte i noen av disse områdene
☐ Underarm, venstre ☐ Underarm, høyre	☐ Brystkasse ☐ Buk/ Mage	

33. Alt i alt, har symptomene nevnt over i del 30-32 vært tilstede i minst 3 måneder? ☐ Ja ☐ Nei

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