Extra-intestinal complications following acute giardiasis

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Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The studies presented in this thesis were done at the Department of Global Public Health and Primary Care, University of Bergen, and the Reasearch Unit for General Practice, NORCE Norwegian Research Centre, Bergen, Norway.

For Paper I and Paper II Guri Rørtveit was the main supervisor, while Nina Langeland was co-supervisor. For Paper III and the completion of this thesis Knut-Arne Wensaas was the main supervisor, with Guri Rørtveit as co-supervisor.

Paper I and Paper II were funded and completed as part of the Medical Student Research Programme at the University of Bergen, Norway. Later, as part of my clinical position at the Department of Dermatology, Haukeland University Hospital, Bergen, Norway, I got the opportunity to resume my research part-time. During the autumn of 2019 I was admitted as a PhD fellow with funding from the Department of Dermatology giving me the opportunity to continue my work in the *Giardia* project completing Paper III and my thesis.

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Bergen, December 2021

Gunnhild Sellevoll Hunskår

Contents

Abstract

Background

Giardia lamblia is a common waterborne protozoan parasite worldwide. A large outbreak occurred in Bergen, Norway, in 2004. It was caused by heavy rainfall overloading the sewage system leading to contamination of the main water reservoir to the city centre. Approximately 48 000 people were exposed. A cohort study was established after the outbreak including 1252 individuals with laboratory confirmed diagnosis of giardiasis and a matched control group. *Giardia* typically causes short-term gastroenteritis, whereas information on long-term complications and extra-intestinal complications was limited before the outbreak.

Aims

The overall aim of the studies in this thesis was to investigate extra-intestinal long-term complications following acute giardiasis.

Methods

As part of the established cohort study **Paper I** and **Paper II** were based on data collected three years after the outbreak and **Paper III** on data collected ten years after the outbreak. Questionnaires were mailed to 1252 patients with laboratory confirmed giardiasis during the outbreak. A control group with 2:1 matching on age and sex was included.

In **Paper I** the main outcome was atopic disease and whether it influences the prevalence of irritable bowel syndrome (IBS) and chronic fatigue (CF) three years after giardiasis. Atopic diseases investigated were asthma and allergy which were self-reported, and the diagnoses were based on questions applied in other studies.

In **Paper II** the main outcomes were excessive daytime sleepiness, insomnia, and level of sleep need three years after infection with *Giardia* compared with a control group. The validated Epworth Sleepiness Scale (ESS) was used for evaluation of excessive daytime sleepiness, insomnia was evaluated by a single question, and sleep need by self-reported hours of sleep to feel rested.

In **Paper III** the main outcome was fibromyalgia ten years after acute infection with *Giardia lamblia*. Fibromyalgia was defined according to the 2016 Fibromyalgia criteria based on the response to the validated Fibromyalgia Survey Questionnaire (FSQ).

IBS and CF were outcome variables in each paper. IBS was defined according to the Rome III diagnostic criteria and CF was defined by the validated Fatigue Questionnaire.

Results

In the three-year follow-up the response rate was 65.3 % (817/1252) among *Giardia* exposed and 31.4 % (1128/3598) among controls. In the ten-year follow-up the corresponding response rates were 50.3% (592/1176) and 30.4% (708/2330).

In **Paper I** we found an association between atopy and both IBS and CF in the control group, but not in the exposed group. Among the *Giardia* exposed with asthma three years after the outbreak, 47.8 % (43/90) had IBS compared with 45.3 % (291/642) among *Giardia* exposed without asthma ($p = 0.662$). Among controls with asthma 23.9 % (32/134) had IBS compared with 12.2 % (114/936) among controls without asthma ($p < 0.001$). The relative risk (RR) for IBS among *Giardia* exposed with asthma was 2.03 (95% confidence interval (CI): 1.45, 2.62) compared with controls with asthma. The RR for IBS among *Giardia* exposed without asthma was 3.80 (95% CI: 3.30, 4.32) compared with controls without asthma. Among *Giardia* exposed with asthma the prevalence of CF was 51.5 % (51/99) compared with 44.9 % (295/657) in *Giardia* exposed without asthma ($p = 0.218$). Among controls with asthma 19.3 % (26/135) had CF compared with 10.7 % (102/949) among controls without asthma ($p = 0.004$). The RR for CF among *Giardia* exposed with asthma was 2.73 (95% CI: 1.98, 3.45) compared with controls with asthma. The RR for CF among *Giardia* exposed without asthma was 4.25 (95% CI: 3.66, 4.85) compared with controls without asthma. For allergy, the results were similar.

In **Paper II**, excessive daytime sleepiness was reported by 31.5 % (245/777) of the *Giardia* exposed compared with 14.1 % (154/1090) among controls ($p < 0.001$) three

years after the outbreak. Mean (SD) self-reported sleep need was 8.0 (1.4) hours among *Giardia* exposed and 7.5 (1.1) hours among controls ($p < 0.001$). Excessive daytime sleepiness and increased sleep need were both found to be independently associated with *Giardia* exposure. In multivariate analysis the adjusted odds ratio (OR) for excessive daytime sleepiness was 1.40 (95% CI: 1.06-1.86). By multiple linear regression analyses the adjusted regression coefficient for sleep need was 0.12 (95% CI: 0.01-0.24) meaning that *Giardia* exposure increased the sleep need with 0.12 hours. Insomnia was reported by 15.4% (125/811) of *Giardia* exposed and 8.8% (98/1116) of controls ($p < 0.001$), but in the adjusted analyses there was no association between *Giardia* exposure and insomnia (OR 0.93 (95% CI: 0.65-1.35)).

In **paper III** we report the prevalence of fibromyalgia ten years after the *Giardia* outbreak. The prevalence of fibromyalgia was 8.6 % (49/572) among *Giardia* exposed and 3.1 % (21/673) among controls ($p < 0.001$). Unadjusted odds for having fibromyalgia was higher for *Giardia* exposed compared with controls (OR: 2.91, 95% CI: 1.72, 4.91), but adjusted for IBS and CF it was not (OR: 1.05, 95% CI: 0.57, 1.95). Among participants without CF the odds for fibromyalgia was 6.27 times higher for participants with IBS than those without (95% CI: 3.31, 11.91) regardless of exposure. Among participants without IBS the odds for fibromyalgia was 4.80 times higher for those with CF than those without (95% CI: 2.75, 8.37). Fibromyalgia, IBS, and CF are conditions known to overlap.

Conclusion

These studies show an association between acute giardiasis and several extra-intestinal complications three and ten years later. We found the studied complications to be highly associated with IBS and CF. These findings provide novel insight into the complexity of long term consequences after infection and will be useful both for patient management and further research.

List of publications

- Hunskar GS, Langeland N, Wensaas KA, Hanevik K, Eide GE, Mørch K, Rortveit G. The impact of atopic disease on the risk of post-infectious fatigue and irritable bowel syndrome 3 years after Giardia infection. A historic cohort study. Scand J Gastroenterol 2012; 47: 956-61.

- Hunskar GS, Bjorvatn B, Wensaas KA, Hanevik K, Eide GE, Langeland N, Rortveit G. Excessive daytime sleepiness, sleep need and insomnia three years after Giardia infection: a cohort study. Sleep Health 2016; 2: 154-8.

- Hunskar GS, Rortveit G, Litleskare S, Eide GE, Hanevik K, Langeland N, Wensaas KA. Prevalence of fibromyalgia 10 years after infection with *Giardia lamblia*: a controlled prospective cohort study. Scand J Pain 2021 Oct 22. doi: 10.1515/sjpain-2021-0122. Epub ahead of print. PMID: 34679267.

The publications are referred to as **Paper I**, **Paper II,** and **Paper III** in the thesis.

Abbreviations

ACR = American College of Rheumatology

CF = Chronic Fatigue

CFS = Chronic Fatigue Syndrome

CI = Confidence Interval

EBV = Epstein Barr Virus

ESS = Epworth Sleepiness Scale

FGID = Functional Gastrointestinal Disorders

FSDC = Fibromyalgia Survey Diagnostic Criteria

FSQ = Fibromyalgia Survey Questionnaire

FQ = Fatigue Questionnaire

IBS = Irritable Bowel Syndrome

MSIS = Norwegian Surveillance System for Communacicable Diseases

MUPS = Medically Unexplained Physical Symptoms

OR = Odds Ratio

PI-IBS = Post-infectious Irritable Bowel Syndrome

RR = Relative Risk

SD = Standard Deviation

SSS = Symptom Severity Scale

WPI = Widespread Pain Index

1. Background

1.1. Giardia lamblia

1.1.1. Microbiology and epidemiology

Giardia species is a waterborne, flagellated, binucleated protozoan parasite that is very common worldwide and is estimated to infect 280 million people annually (1, 2). Giardiasis has been part of the World Health Organization initative of Neglected diseases since 2004, which is a list of diseases that persist under poverty in developing counties (3). In developed countries the prevalence of giardiasis ranges from 3 % to 7 %, whereas in developing countries it ranges from 20 % to 30 % with some reports in populations of 100 % (4). In the Nordic countries the estimated prevalence of *Giardia lamblia* is 3 % in the asymptomatic general population and 6 % in patients with gastrointestinal symptoms (5). *Giardia* is relatively rare in Norway, and has probably been undetected in sporadic single cases as this infection is mostly being considered as traveller's diarrhea or prevalent among immigrants (6). There has been a rising incidence of reported *Giardia* infections in Norway during the last 20 years partly because of increasing travelling activity to endemic areas, but also improved detection of *Giardia lamblia* with PCR diagnostics (7). In 2019 there were 578 cases of giardiasis reported in Norway, with the majority of traceable cases being infected abroad (8). Outbreaks of giardiasis are not uncommon worldwide, with contaminated drinking water being the main cause of transmission (9).

Giardia is common in animals, and the species *Giardia lamblia* is found in humans (9). *Giardia* affects the upper small intestine and is transmitted through contaminated water or food, or fecal/oral transmission (4). *Giardia lamblia* is one of six *Giardia* species and is divided into eight recognized genotypes or assemblages, A to H. Assemblages A and B causes the human infection of giardiasis (1). The infection spreads by cysts and a limited number (up to ten cysts) is needed for transmission of giardiasis (10). In the encysted form *Giardia* is highly resistant and can survive for months, particularly in water (2). After ingestion of cysts that survive through the ventricle, the second form of the parasite which is called a trophozoite emerge from the cysts in the upper small intestine after being exposed to stomach acid, bile, and

trypsin in the duodenum (1, 10). The trophozoite is the disease-producing form of *Giardia lamblia* and can swim freely in the duodenum and ileum, but also attach to the intestinal epithelium via a ventral adhesive disc (2). This attachment resists peristaltic expulsion and the production of parasitic products is the cause of the symptomatic disease, but also host immunological responses affect the intensity and duration of infection (11). The incubation period for G*iardia lamblia* is 6-15 days (1). Return to encystation begins when the parasite is transported further down the gastrointestinal tract being exposed to increased bile and alkaline pH, which leads to protection and survival for further transmission after excretion (12).

Giardia lamblia is synonymous with the terms *Giardia duodenialis* and *Giardia intestinalis*. Infection with *Giardia lamblia* causes giardiasis that can manifest itself differently, from asymptomatic disease to acute or chronic disease with diarrhoea, epigastric pain, flatulence and bloating, and in the more prolonged cases weight loss and malabsorption (1, 10). Giardiasis is usually a self-limiting infection, but re-infection and chronic infection can occur (4). Metronidazole for seven days is first-line treatment for giardiasis, but this fails in up 20 % of cases (10). Other treatments are available, but growing antibiotic resistance has been shown in *Giardia* (10).

1.1.2. Complications/ post-infectious complications

Complications after infectious diseases can be divided into acute and long-term complications, and for a gastrointestinal infection such as giardiasis further into intestinal and extra-intestinal complications. Why some individuals experience prolonged infection and long-term or chronic sequelae is not fully understood, but studies indicate a possible association to the virulence of the *Giardia* strain, host nutritional intake, co-infecting enteropathogens, the composition and function of host microbiota and host genetics and immunity (13).

As with all gastrointestinal infections causing diarrhea, the risk of dehydration, electrolyte disturbances or weightloss is great during the acute phase, but will be relieved and resolved by either spontaneous recovery or eradication of the infection

(14). Other complications that are relieved by eradication include hypokalemic myopathy and skin allergies (4).

Among children, particularly in developing countries, *Giardia* infection is associated with malabsorption, iron-deficiency anemia, anorexia or malnutrition, failure to thrive, and consequently poor cognitive function (4, 14).

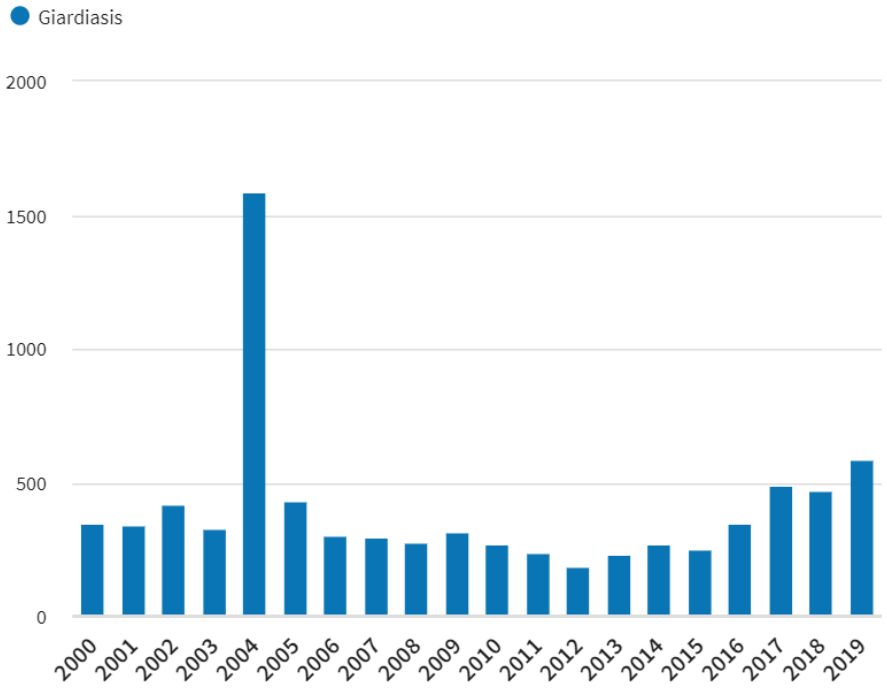
In a study from 2011 it was estimated that 1/3 of *Giardia* patients experience long-term extra-intestinal symptoms, making post-infectious complications not as uncommon as previously perceived (15). Complaints of eye, skin, joint and urinary symptoms were all reported in this study, with debut within 30 days of *Giardia* infection. Most of the symptoms had resolved within 30 days after onset of the extra-intestinal symptoms.

Ocular pathologies reported after giardiasis include iridocyclitis, choroiditis, retinal hemorrhages, and pigmented degeneration of the retina (4). Retinal changes are mostly seen in children and do not always resolve with eradication of infection. Post-infectious arthritis is documented, but scarce when one take account for how common giardiasis is worldwide. It has not been associated to HLA-B27 positive spondyloarthropathy, as is often seen in post-infectious arthritis associated to other enteric pathogens.

1.1.3. The Bergen outbreak in 2004

Cases of giardiasis in Norway have risen to 4-600 cases annually the last few years, with the lowest incidence during the last 20 years in 2012 with 179 cases (16). In 2004 there were 1580 registered giardiasis cases, mainly explained by the *Giardia* outbreak in Bergen. During the outbreak there were 1252 cases with verified giardiasis that could not be linked to foreign travel. It was estimated that 48 000 people were exposed to the contaminated water and 2500 patients received treatment with metronidazol (17).

Figure 1: *Giardia* cases in Norway reported to Norwegian Surveillance System for Communacicable Diseases (MSIS) from 2000-2019 (16).



This outbreak was a unique possibility to study giardiasis and possible complications in a community-based study with a well-defined exposure. Several papers have been published based on data from this outbreak offering comprehensive insight on long-term post-infectious complications following acute giardiasis. Studies have shown a higher prevalence of irritable bowel syndrome (IBS) and chronic fatigue (CF) among *Giardia* exposed compared with the control group three, six and ten years after infection (18-20). It was a higher prevalence of overactive bladder syndrome and functional dyspepsia six years after *Giardia* infection compared with controls (21). The association to overactive bladder syndrome dissipates when controlled for IBS, CF, and functional dyspepsia. The prevalence of perceived food intolerance was higher among the *Giardia* exposed compared with controls three years after infection (22). In addition to high prevalences of IBS and functional dyspepsia three years after

infection, there was also a high prevalence of other gastrointestinal symptoms i.e., bloating, diarrhea, nausea, foul smell, with a high degree of overlap between the disorders (23). Ten years after infection the *Giardia* exposed group experienced lower quality of life compared with controls and this effect was mediated by IBS and CF (24). Other studies after the outbreak, but not part of the extensive follow-up cohort study, have shown high levels of post-infectious fatigue and abdominal symptoms two years after infection, with protracted and severe giardiasis as a risk-factor for developing these symptoms (25, 26). Also, associations between giardiasis and chronic fatigue syndrome five years after infection were demonstrated, but with reduction of self-reported fatigue at five years compared with three years after giardiasis (27).

1.2. Atopy

Atopy is a predisposition to develop an exaggerated immune response to different allergens (28). It is considered a type I hypersensitivity reaction which is an immediate reaction that leads to overproduction of immunoglobulin E (IgE) (29). Atopic diseases include nasal allergic rhinitis or hay fever, allergic conjunctivitis, atopic eczema, allergic bronchial asthma, food allergies, and in rare cases anaphylaxis. The most common manifestations are asthma and hay fever. Asthma is a chronic inflammatory condition of the respiratory tract causing coughing, wheezing or tightness of the chest. Rhinitis or hay fever can cause a running nose or itching of eyes and nose (28). An individual with atopic disease may have several atopic manifestations either simultaneously or at different times during a lifetime (30, 31).

The exact etiology of atopy is unknown, but development of atopic disease is considered multifactorial. They include genetic predispositions, immunological mechanisms, socioeconomic status, and environmental factors such as pollution, but also the “hygiene hypothesis” that suggests that a lack of exposure to microbes at an early age can cause development of atopic disease because of failures in immune system functionality (29, 32).

Atopy is common in the general population, and is estimated at 10-30 % in developed countries, commonly with an accumulation of cases in families (28). There are no

national data on the prevalence of asthma or allergy in Norway, but smaller studies on children and adolescents have shown prevalences ranging from 18 – 26 % (30, 31, 33). For European adults the prevalence of allergic rhinitis is 23 % (34).

1.2.1. Atopy, irritable bowel syndrome and chronic fatigue

It has previously been shown that patients with asthma and hay fever have a higher prevalence of IBS (35, 36). In IBS patients with atopy, it was shown increased proximal small intestine permeability compared with IBS patients without atopy, and among the subgroups of IBS patients studied, proximal small intestinal permeability was increased in patients with postinfectious IBS (36). One study showing a high incidence of IBS among adults with atopy presented the expression “atopic IBS” as a subgroup (37). Studies indicate a high prevalence of allergy among patients with CFS and a newer study also suggest a higher risk of CFS among patients with atopy, particularly among patients with multiple atopic syndromes (38, 39).

1.3. Sleep

Sleep disturbances and disorders are common and affect the individual, but also have consequences for society (40). Sleep is considered important for good health. Insomnia, sleep apnea, and restless legs syndrome are the most common sleep disorders.

1.3.1. Excessive daytime sleepiness

Patients with hypersomnia disorders complain of excessive sleepiness during the day (41). There is difficulty staying awake during daytime and periods of unintended sleep may occur. It can be caused by disorders such as narcolepsy, obstructive sleep apnea syndrome, movement disorders during sleep, and idiopathic hypersomnia (42). Excessive sleepiness is distinguished from fatigue with the main feature of fatigue being tiredness, exhaustion and lack of energy that can be relieved by rest, whereas sleepiness gives a decreased mental and physical capacity with the tendency or need to fall asleep which may not give the desired relieve (42). These conditions have been shown to overlap (43).

The prevalence of excessive daytime sleepiness varies considerably from 0.5 - 35.8% in studies. Some of this variation can be explained by this partly being subjective symptoms and the use of various definitions. Studies on the general population have shown a prevalence of 2.5 % in Japan and 8.7 % in the United States (44, 45). The Epworth Sleepiness Scale (ESS) is a validated self-administered questionnaire that measures the general level of daytime sleepiness (46).

1.3.2. Insomnia

The most common sleep disorder is insomnia (40). It is defined as a lack of sleep or insufficient sleep and not feeling rested. It can be caused by trouble falling asleep, poor sleep maintenance, waking up too early, or the individual experiencing their sleep of poor quality (41). Insomnia is diagnosed by the patient's subjective experience and how the sleep disturbance is affecting daytime functioning. This sleep condition can be considered primary or secondary, with secondary insomnias also being referred to as comorbid insomnia. Primary insomnias are typically caused by specific stressors, behaviours, or inadequate sleep hygiene. Comorbid insomnia is defined as a symptom of a medical or psychiatric illness, substance abuse or another sleep disorder.

Insomnia symptoms are found in about a third of the general population worldwide, and approximately 6 % are given a diagnosis of insomnia by a doctor (47). In Norway the prevalence of insomnia diagnosis is 12 %, and there is an increase in diagnosed insomnia symptoms in the last decades (48, 49).

1.3.3. Sleep need

The amount of sleep needed varies greatly among individuals, and also depends on sleep quality (50). A person's sleep need is met if it they feel rested during the day. The normal range for sufficient sleep is between 6 and 9 hours, with a mean sleep duration of 7-7.5 hours. A study on sleep in the general population aged 40-45 years old in Hordaland, Norway found that the mean subjective sleep need was 7h 16 minutes in men and 7h 45 minutes in women (51).

1.3.4. Sleep and infection

A limited number of studies have shown prior infections to be associated with sleep disturbances and changes in sleep pattern. In a study of 12 patients with Epstein Barr Virus (EBV) all developed daytime sleepiness weeks to months after onset of clinical symptoms, and a case-control study on university students with EBV showed that those infected needed significantly more sleep that the control group up to 150 days after diagnosis (52, 53). An assessment of 22 patients 13-36 months after acute SARS-virus infection showed a tendency of disturbed and nonrestorative sleep and fatigue, among other long-term symptoms such as pain and weekness, all to a degree that led to reduced work participation more than one year after infection (54). Streptococcal throat infection has been associated with the development of narcolepsy with cataplexy, and restless legs syndrome has been shown after streptococcus and mycoplasma infection in children (55, 56). Restless legs syndrome has also been reeported after infections with several other pathogens, such as borrelia, cytomegalovirus, and in chronic infections such as AIDS and hepatitis (57).

1.3.5. Sleep, irritable bowel syndrome and chronic fatigue

Sleep disturbances are common in patients with IBS and have been shown to be related to the symptom severity (58). Excessive daytime sleepiness is associated to functional gastrointestinal disorders, such as IBS (59). In one study IBS patients had increased daytime sleepiness and insomnia compared with healthy controls (60). Patients with both IBS and functional dyspepsia also had more insomnia, but also higher ESS scores. In a study on patients in a tertiary care GI clinic 48 patients had IBS as the primary diagnosis (61). Compared with other GI diagnoses, the IBS patients had the highest frequency of poor sleep quality and clinical insomnia, 72 % and 51 % respectively. The association between IBS and sleep disturbances has been acknowledged, but it is still unclear which comes first or if this relationship goes both ways (62).

Daytime sleepiness and chronic fatigue have been shown to co-exist, but it has been questioned whether one can surely separate these conditions because of numerous

definitions and tools for assessment (63, 64). Tiredness is a common complaint and often used synonymously with sleepiness and fatigue. A study found that CFS patients had higher levels of subjective sleepiness and fatigue compared with a healthy control group, but they had normal sleep onset latency and no objective signs of being sleepy (43).

1.4. Fibromyalgia

Fibromyalgia is a common rheumatologic disorder of chronic, generalized pain where a distinct causality to the symptoms has not been found (65, 66). In addition to pain, patients with fibromyalgia often report fatigue, sleep disturbances, morning stiffness, headaches and anxiety (67). Fibromyalgia patients is a group with high healthcare utilization and high levels of comorbidity, including different pain conditions and diseases of the circulatory system, diabetes, anxiety, depression, IBS and sleep disorders (68). Several classification criteria and different questionnaires with and without need of clinical examination have been developed with the American College of Rheumatology (ACR) criteria from 1990 being the leading diagnostic criteria as a base for further investigation and development of new and more precise criteria for this disorder (67, 69).

The prevalence of fibromyalgia differs based on the method and criteria chosen to detect the disorder. Because of several changes and improvements to the diagnostic criteria it can be challenging to compare studies and their results. A relatively recent and large review including studies published up to November 2015 estimated a prevalence of 1.78 % in the general population worldwide, with a predominance in women estimated to 3.98 % (70). The same study found the prevalence of fibromyalgia in Europe to vary from 0.29 % in Germany to 11.10 % in Turkey, with a total European prevalence of 2.64 %. Different methods and criteria were used according to when the studies were executed, but most often it was different versions of the American College of Rheumatology (ACR) criteria. The prevalence was 2.32 % when only looking at studies using the different ACR criteria (70). A longitudinal population health study from 1995-1997 in Norway investigated fibromyalgia among other conditions, and found the prevalence in the general population to be 3.2 %, with

5.2 % among females compared with 0.9 % among men (71). This is in line with the European prevalence and gender distribution.

1.4.1. Definition and diagnosis

The diagnosis of fibromyalgia evolved during the 20th century and there was increasing interest in pain syndromes leading to different definitions and the use of several imprecise criteria sets. It was desirable with a consensus on the definition of fibromyalgia as well as new and methodologically stronger criteria for classification (67). The ACR 1990 criteria was the first diagnostic criteria based on a blinded study on fibromyalgia and based the diagnosis on a combination of widespread pain and tenderness in ≥ 11/18 specific tender points (67). Widespread pain was defined as pain in the right and left side of the body, above and below the waist as well as axial skeletal pain. The ACR 1990 criteria were later criticized for only considering pain as a symptom of fibromyalgia and also not providing the possibility of grading the severity of pain or follow change in symptoms as they were dichotomous (72, 73). The criteria were dependent on clinical examination which was considered a possible problem because tender point examination was rarely done by practicioners and also made room for incorrect execution. As a consequence, a new set of diagnostic criteria including other symptoms in fibromyalgia and symptom severity was approved by the American College of Rheumatology in 2010 (72). The ACR 2010 fibromyalgia diagnostic criteria included a widespread pain index (WPI) with a score of 0-19 based on the number of painful body areas and a symptom severity scale (SSS) focusing on fatigue, waking up unrefreshed and cognitive dysfunction with a total scoring range of 0-12. Symptoms also had to be present for at least three months and no other disorder present to explain the pain. Still, the criteria called for a clinical examination from a physician. A modification was therefore presented in 2011, with the additional development of the Fibromyalgia Survey Questionnaire (FSQ) which could be completely patient self-administered (74). The modification to the criteria included the Fibromyalgia Symptom scale for measurement of severity with a score of 0-31 which was a combination of the WPI and SS scale, and three new symptoms for evaluation; headache, pain in lower abdomen and depression symptoms during the

last six months. The development of the questionnaire and modification to the criteria made them suitable for research in larger epidemiological studies.

An updated version of the criteria in 2016 was based on validation studies comparing the different sets of criteria as well as other reports on the previous criteria (75). The new criteria adjusted the cutoff on the WPI and SSS, brought back the consept of generalized pain with some modification of regions and a diagnosis of fibromyalgia could co-exist with other illnesses. The 2016 Fibromyalgia criteria are met if: 1) Either WPI ≥ 7 and SSS score ≥ 5, or WPI 4-6 and SSS score ≥ 9; 2) Generalized pain defined as pain in at least four out of the following five regions based on the WPI: left upper region, right upper region, left lower region, right lower region and axial region; 3) Symptoms have been generally present for at least three months. The Norwegian version of the FSQ has been validated (73).

1.4.2. Fibromyalgia and infection

There is not clear support in the literature for fibromyalgia as a post-infectious condition or infection as an etiologic factor in development of fibromyalgia (76, 77). Research is scarce, but some infections have been investigated as possible triggers for fibromyalgia: Hepatitis, HIV-infection and Lyme disease (77). Higher prevalences of fibromyalgia is found in patients with chronic or inactive hepatitis B, chronic hepatitis C and HIV (78-81). Lyme disease have been suggested as a possible trigger for fibromyalgia, but conclusions are unclear as the symptoms of Lyme disease and symtoms after treatment of this infection can be very similar to fibromyalgia making these disorders hard to distinguish (76, 82). Still, more investigation needs to be done to understand and confirm these associations.

1.4.3. Fibromyalgia, irritable bowel syndrome and chronic fatigue

There is great overlap in prevalence between IBS, CF and fibromyalgia (83, 84). IBS and fibromyalgia are found to predict each other, but CF is not (84). Fatigue is shown to be common in patients with IBS, and the fatigue to be more severe in patients with more severe IBS symptoms (85, 86). Fibromyalgia and IBS are found to co-exist, with presence of fibromyalgia associated to the severity of IBS (87). A study found

that among female fibromyalgia patients 32 % had IBS, and among IBS patients regardless of sex 31.6 % had fibromyalgia (88). A female predominance of the coexistence of IBS and fibromyalgia has been shown (89). Fatigue is very common in patients with fibromyalgia and vice versa, and in the revised criteria for fibromyalgia fatigue has been included as one of the symptoms (90, 91).

IBS, CF and fibromyalgia are the most prevalent disorders included in the term medically unexplained physical symptoms (MUPS) and also those most studied. MUPS is a term used to describe different syndromes not explained by measurable pathology, but with overlapping symptoms and symptom patterns (92, 93). Other terms for these symptoms and symptom patterns are medically unexplained symptoms, functional somatic syndromes or disorders, and bodily distress syndrome (93). MUPS is common and seen in both primary care and most medical specialties such as rheumatology, gastroenterology, infectious diseases and neurology (94-96). These symptoms can largely influence the patient's life and be of great burden for the patient. They are difficult to manage for the physician, especially as there often are nonspecific symptoms and no clear findings on testing or examinations (95).

There is ongoing discussion whether MUPS should be considered different presentations of one common condition or as distinct entities (97). These opposite understandings of the syndromes have led to the distinction between "lumpers" or "splitters". A less divisive understanding of MUPS is proposed as seeing this as a wide collection of symptoms with possible shared etiology that can also be divided into subgroups (96).

1.5. Irritable bowel syndrome

IBS is characterized by abdominal pain or discomfort associated with stool changes or defecation over a time period of at least six months. IBS is one of several functional gastrointestinal disorders (FGID) (98). FGID include a variety of symptoms and disorders from the gastrointestinal tract, and the criteria for different diagnoses suitable for research and patient management are developed in an ongoing international process led by the Rome Foundation. The Rome diagnostic criteria has

been revised and validated several times with the latest being the Rome IV diagnostic criteria developed and validated in 2016 (99, 100).

The pathophysiology of IBS is not completely understood with inconsistent measurable pathologic findings. Several factors, including changes in gut microbiome, intestinal permeability, gut immune function, motility, brain-gut interaction and visceral sensation, have been found to be involved in the development of IBS (101). Higher levels of anxiety and depression are also shown in patients with IBS (102).

IBS has a large impact both on the individual and socio-economic level with reduced work productivity and health-related quality of life, and increased doctor-seeking behavior leading to higher expanditure for medical testing and procedures (103).

IBS is highly prevalent and the most commonly diagnosed gastrointestinal condition with prevalences worldwide ranging from 1.1 % to 45 % depending on the country and criteria used for diagnosis (104). A recent study found the worldwide prevalence of IBS according to the Rome IV diagnostic criteria collected by internet surveys to vary from 1.3 % to 7.6 %. This is lower than in earlier studies and is primarily due to the Rome IV diagnostic criteria being more restrictive than earlier versions (105). There is a predominance among females with an OR of 1.67 for women compared with men, and a decrease in prevalence with higher age. By use of the Rome III diagnostic criteria the prevalence has been estimated in Western countries to range from 10-18 % (106). In Norway the estimated prevalence of IBS was 8 % in 2006 by use of the Rome II diagnostic criteria (107).

1.5.1. Definition and diagnosis

The diagnosis of IBS is based on the patient's symptoms, and the diagnosis can be made by the administration of questionnaires (108). The definition and diagnosis of IBS has been under discussion for many years, and the first set of criteria, the Manning Criteria, were published in 1978 (109). The Rome criteria was first developed by consensus and symptom-based approach in 1988, later with several modifications to the questionnaire and criteria up to the latest version in 2016, which

is the Rome IV diagnostic criteria (98, 100). In the *Giardia* cohort studies the Rome III diagnostic criteria were used. They define IBS as recurrent abdominal pain or discomfort at least three days per month for at least three months and improvement with defecation and/or change in frequency and/or consistency of stools, and onset at least six months prior to diagnosis (98). The Rome IV diagnostic criteria diagnose IBS by recurrent abdominal pain at least one day per week in the last three months, related to defecation and/or change in frequency and/or consistency of stool, also with onset of symptoms at least six months prior to diagnosis (100). The newest criteria are more stringent with weekly rather than monthly symptoms, symptoms described as pain rather than discomfort and that abdominal pain and defecation are only associated but not required to cause improment in symptoms (100). These changes have lead to lower prevalence rates of IBS with the change from monthly to weekly symptoms having the largest impact (100, 105)

1.5.2. Irritable bowel syndrome and infection

IBS is a well-known complication after gastrointestinal infections (110-114). Post-infectious IBS (PI-IBS) has been investigated and found to be a distinct subgroup with a predominance of diarrheal symptoms compared with IBS in individuals without prior infection (115). A study looking at characteristics of patients with IBS found that 6-17 % of patients experienced onset of IBS after acute gastroenteritis (116). In patients with infectious gastroenteritis 4-36 % have developed post-infectious IBS, with bacterial, protozoan and helminth infections leading to particularly prolonged IBS symptoms (117). IBS has been shown after bacterial infection with Campylobacter, Salmonella, Shigella, E-coli and Clostridium difficile (110-114, 118). IBS has been shown after viral infection with norovirus, but the duration is shorter than after bacterial infections (110, 119).

1.6. Chronic fatigue

Fatigue is a common symptom that varies in severity and affects 30-50 % of the adult general population (120). Fatigue with a duration of more than six months is characterized as chronic fatigue (CF) (121). Chronic fatigue syndrome (CFS) is a debilitating condition characterized by physical and mental fatigue limiting function

as its main symptom, but also including a range of physical and psychological symptoms where the diagnosis of CFS can only be made after exclusion of other medical or psychiatric causes for fatigue (121, 122). No measurable pathology has been detected in CFS and the exact cause of this syndrome is still unknown (123). Still, infections, immunological dysfunction, genetics, and social factors are considered possible contributing causes for development of these symptoms (124). A hypothesis is that both CF and CFS are regarded as different expressions on a continuum of fatigue (120). The prevalence of CFS is estimated at 0.5-2.5 % (123, 125). Chronic fatigue is more prevalent and has been estimated to affect 11% of the Norwegian general population which is in line with detection of 11.3 % in a British study, whereas 30.5 % were considered to have CF in the Dutch general population (120, 126, 127). A systematic review of the prognosis of these conditions showed a recovery rate of 54-94 % for CF among children and less than 10% for CFS among adults during the follow-up period (121).

1.6.1. Definition and diagnosis

CF is defined as persistent fatigue of a certain severity for at least six months. In the *Giardia* cohort studies CF is based on the responses to the Fatigue Questionnaire (FQ) which measure physical and mental fatigue (128). Chronic fatigue is a significant part in the more stringent diagnosis of CFS. Different case definitions and diagnostic criteria for CFS have been developed, but there is not extensive comparative evalutaions and validation studies are considered weak (124). The main symptom is mental and physical fatigue not being relieved by normal rest. A review on CFS summarises that for the diagnosis of CFS it is necessary to recognize the fatigue symptoms, perform physical examination to exclude other medical or psychiatric causes for the symptoms and apply restricted laboratory testing (123).

1.6.2. Chronic fatigue and infection

CF and CFS are known complications after infections such as mononucleosis, hepatitis, and viral meningitis, among others (129, 130). After the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003 persistent fatigue was reported, and also Coronavirus disease 2019 (COVID-19), caused by SARS-Coronavirus-2 (SARS-

COV-2) is suggested to be a contributing factor for development of fatigue (54, 131). Data on associations between different infectious agents and development of fatigue is not unambigously supportive of this causality. Theories of persistent infections, abnormal persistent immune response, neuroendocrine changes or genetic predisposition as a cause for fatigue have not been successfully proven (123).

2. Aims of study

The main objective of this thesis was to investigate extra-intestinal complications three and ten years after the *Giardia lamblia* outbreak in Bergen. Norway, 2004.

Paper I was based on previous findings from the outbreak showing high prevalence of irritable bowel syndrome and chronic fatigue three years after *Giardia* infection. The aim of this paper was to investigate whether atopic disease influence the prevalence of IBS and CF after giardiasis.

In **Paper II** the aim was to investigate whether prior infection with *Giardia lamblia* was associated with excessive daytime sleepiness, insomnia, and level of sleep need among *Giardia* exposed compared with a control group three years after infection

In **Paper III** the aim was to investigate whether acute infection with *Giardia lamblia* was associated with fibromyalgia ten years after infection and whether fibromyalgia was associated with IBS and CF in this setting.

3. Materials and methods

3.1. Setting and study design

Bergen, Norway, experienced an outbreak of *Giardia lamblia* during the autumn of 2004 (17). The outbreak was recognized with a rise in cases of diarrhea with discovery of *Giardia lamblia* in samples (17). The outbreak followed a period of heavy rainfall overloading the sewage system and causing contamination of the main water reservoir serving the central parts of the city. Approximately 50 000 inhabitants received water from the reservoir, in addition to educational insititutions, workplaces and other facilities (17). The water supply had insufficient water treatment to secure a safe hygenic barrier. Prescription data showed that about 2500 were treated for giardiasis during the outbreak, and 1252 had a laboratory confirmed diagnosis. This outbreak was unusual in Norway. Larger outbreaks of giardiasis are rare in Europe, and there is normally a low prevalence of *Giardia lamblia* in the Nordic countries (5).

A historic cohort study was set up following the *Giardia*-outbreak. Questionnaires were mailed to all 1252 patients who had laboratory confirmed giardiasis during the outbreak and a 2:1 control group matched by age and sex three, six and ten years after the outbreak. **Paper I** and **Paper II** of this PhD-project were based on data collected three years after the outbreak. **Paper III** used data collected after ten years.

3.2. Participants

The starting point for this study was the 1252 patients with positive fecal test for *Giardia lamblia* during the outbreak. They constitute the exposed group at both three- and ten-years follow-up.

The control group was randomly selected among inhabitants in Bergen and matched on age and sex to the exposed participants with a 2:1 ratio. The control group consisted of 2504 participants. They were selected from the same area as the exposed in order to make the groups more similar with regard to background variables. When chosing controls from the same area as the outbreak there would be a risk of including *Giardia* cases who were not verified by testing. To somewhat make up for

this possible misclassification controls who reported giardiasis during the outbreak were excluded. The initial response rate in the three-year follow-up study was 34.4 % (862/2504) and it was decided to expand the control group by additionally sending the questionnaire to another two matched controls for the 547 exposed where none of the first two matched controls had responded. As a result we added 1094 individuals to the control group, for a total of 3598.

In the ten-year follow-up the study population included the same 1252 *Giardia* exposed individuals and the initial control group of 2504, but participants under the age of 18 were excluded.

3.3. Variables

3.3.1. Exposure

Infection with *Giardia lamblia* with a positive fecal test during the outbreak in 2004 was the exposure in all papers. Exposure was dichotomized into *Giardia* exposed and controls for comparison.

3.3.2. Demographic variables

Age and sex were obtained for all participants at all measuring points. In addition, they were asked about marital status, education, source of income and in the three-year follow-up if they were students during the outbreak. Age, sex, marital status, and education were in all papers considered possible confounders, in addition source of income was considered a possible confounder in **Paper I and Paper II**.

3.4. Questionnaires and outcome variables

3.4.1. Irritable bowel syndrome

Throughout all three papers, IBS was one of the outcome variables. IBS was included due to clinical observations of persisiting gastrointestinal symptoms during and after the outbreak in 2004 (26). This was also shown in early studies after the outbreak (26, 132). In the early studies gastrointestinal symptoms were examined by general questions on abdominal complaints, but at the three year follow-up study it was decided to use a preexisting questionnaire for a more thorough and standardized

investigation of these symptoms (98). The Rome III diagnostic criteria were published in 2006 and were used to define IBS in the upcoming studies. This questionnaire was not validated at the time of implementation, but this has later been performed with modest results in predicting the diagnosis of IBS (133). The Norwegian version was translated by the research group (20).

Before the three year follow-up, which **Paper I** and **Paper II** are based on, the association between *Giardia lamblia* and persistent abdominal symptoms was established in previous studies (26, 132). Also, when the data for **Paper III** were collected the association between acute giardiasis and IBS three and six years after the outbreak had been published (18, 20).

IBS was defined according to the Rome III diagnostic criteria (98). A positive diagnosis requires the presence of recurrent abdominal pain or discomfort for at least three days per month in the last three months with two or more of the following criteria to be met: 1) Improvement with defecation; 2) onset associated with a change in frequency of stool, 3) onset associated with change in form (appearance) of stool. Also, onset of symptoms had to be at least six months prior to questionnaire response.

In **Paper I** IBS was investigated in association to atopy, in **Paper II** in association to sleep disturbances and in **Paper III** in association to fibromyalgia.

3.4.2. Chronic fatigue

CF was investigated in all papers for this thesis. Clinicians reported fatigue as a long-term complaint from patients previously exposed to *Giardia* during the outbreak and after eradication of the infection. Fatigue was therefore included in a study two years after the outbreak and a high prevalence of fatigue among *Giardia* exposed was reported (26). There was also a strong association between fatigue and abdominal symtoms. Abdominal symptoms were more likely after acute gastroenteritis, but the detection of fatigue was more surprising.

To investigate fatigue in the following studies the validated Fatigue Questionnaire (FQ) was chosen (128). This questionnaire was previously translated to Norwegian,

and had been used in a study on fatigue in the general population (126). This questionnaire consists of 11 questions that measure physical and mental fatigue. Each question had a four item Likert-type scale to describe the severity of fatigue symptoms which was dichotomized. CF was defined as a score of four or more. Also, fatigue had to have been present for at least the last six months. For the questionnaire to be accepted there had to be a response to at least seven of the 11 questions, and unanswered questions was scored as the mean of all responses to that question.

We investigated CF, and not CFS which is a clinical diagnosis. Prior to analyzing data for **Paper I** and **Paper II,** CF was shown to be associated to giardiasis three years after infection, and prior to **Paper III** it was shown to also be a long-term complication ten years after infection (19, 20).

3.4.3. Atopy

In **Paper I** atopic disease was investigated in relation to IBS and CF after giardiasis. Atopic disease included asthma and allergy, with allergy defined as hay fever or nasal allergy. Clinicians reported after the outbreak of *Giardia lamblia* that asthma and allergy seemed to give prolonged abdominal symptoms in this group of patients.

For the detection of atopy we included four questions. Asthma was defined by the response to three questions: “Have you or have you had asthma?”, with follow-up questions “if yes, has this been confirmed by a medical doctor” and “have you used any asthma medications in the last month?”. Answering yes to the entry question defined the participant in the asthma group. If the answer to this question was “no”, they could still be included in the asthma group if answering confirmatory to asthma being diagnosed by a medical doctor. Participants answering “uncertain” to the entry question could be included in the asthma group if they answered “yes” to the follow-up questions. For allergy only one question was asked: “Have you or have you had hay fever or nasal allergy?”. The entry question on asthma and the question on allergy had answering options: “yes”, “no” and “uncertain”, whereas the follow-up questions had “yes” and “no”. We did not have validated questionnaires on atopy in our study, but the questions on asthma had been used previously (134).

3.4.4. Sleep

Excessive daytime sleepiness, insomnia and sleep need in association to *Giardia* infecton three years earlier was investigated in **Paper II**. Our study had previously shown a high prevalence of fatigue after giardiasis, and we also wanted to examine if sleep was affected by the infection (26).

3.4.4.1. Excessive daytime sleepiness

Our first outcome on sleep was excessive daytime sleepiness evaluated by the Epworth Sleepiness Scale (ESS) which is a self-administered questionnaire to detect subjective daytime sleepiness (46). The Norwegian version of this questionnaire has previously been used in a general adult population and the Norwegian version is validated (135, 136). This questionnaire consists of eight questions with description of different daily situations where the participant would rate the probability to doze off. Each question was scored on a Likert-type scale ranging from 0-3. The ESS total score ranged from 0-24 with values ≥ 11 indicating excessive daytime sleepiness. A missing answer on any of the eight questions would exclude the participant/questionnaire from evaluation on daytime sleepiness.

3.4.4.2. Insomnia

Insomnia was evaluated by a single question: “During the last month, how often have you experienced insomnia?”, It was scored in rising frequency by four options and analysed dichotomized with “more than once a week” as the cut-off for diagnosing insomnia.

3.4.4.3. Sleep need

Sleep need was addressed by the question; “How much sleep do you need to feel rested?”. This measure was self-reported, and participants would estimate sleep need by hours with one decimal accepted.

3.4.5. Fibromyalgia

Paper III focused on fibromyalgia ten years after infection with *Giardia lamblia*. Our group has previously showed an association between giardiasis and IBS and CF

ten years after the outbreak (19). Fibromyalgia is considered a MUPS disorder, and is frequently studied with IBS and CF as a triad of syndromes which have shown to be associated and overlap with each other (94, 137, 138). Considering IBS and CF were thoroughly examined in our study previously, we decided in the ten-year follow-up to include a questionnaire on fibromyalgia to examine whether fibromyalgia was associated to giardiasis like the other MUPS conditions examined.

In the ten year follow-up we could investigate fibromyalgia using the validated FSQ, which is a completely patient administered questionnaire (74). The Norwegian version of this questionnaire has been validated (73). Fibromyalgia was defined according to the 2016 revision of the 2010/2011 fibromyalgia diagnostic criteria (75). The FSQ consists of the widespread pain index (WPI) and the symptom severity scale (SSS). WPI is a questionnaire to evaluate pain in 19 body areas during the last week scored 0-19. SSS consists of six questions on severity of fatigue, waking up unrefreshed and cognitive impairment during the last week scored 0-3, and presence of headaches, pain or cramps in lower abdomen and depression during the last six months scored 0-3. The total score of the SSS ranges from 0 to 12.

The 2016 revised fibromyalgia diagnostic criteria may diagnose fibromyalgia in adults when these criteria are met (75):

1. WPI $\geq$ 7 and SSS score $\geq$ 5, OR WPI 4-6 and SSS score $\geq$ 9.
2. Generalized pain defined as pain in at least four out of the following five regions based on the WPI: left upper region, right upper region, left lower region, right lower region and axial region. Jaw, chest and abdominal pain are not included in the generalized pain definition.
3. Symptoms have been generally present for at least three months.

Participants with partially missing answers were managed according to the following rule: If the total score of given answers could surely decide on group affiliation they were placed in the particular group and not registrered as missing on this questionnaire. True missing were those who either answered no questions, or answered in a way where group affiliation could not be decided.

3.4.6. Analyses and statistics

In all papers the χ^2 test was applied to test differences between proportions. In **Paper I** confounding and interactions were evaluated by logistic regression and the outcome measure of odds ratios (OR) were transformed into relative risks (RR) by use of the formula developed by Zhang and Yu, with strength and significance of associations given by 95% confidence intervals (CI) (139). All analyses were done adjusted for the matching performed when the groups were assembled. Confounders evaluated were age, sex, marital status, source of income and level of education. Modifying effects of the outcome variables were examined by including and testing corresponding interaction terms in the logistic regression models.

In **Paper II** the *T*-test was applied to compare means. All analyses were done adjusted for age, sex, marital status, education, source of income, and student status in 2004. Logistic regression analysis was used to investigate associations between exposure and outcome measures, with results given as ORs and 95 % CI, and multiple linear regression analysis performed with results given as hours. Regression was also used to estimate differences in mean and standard deviation (SD) between the groups.

In **Paper III** binominal logistic regression was applied to investigate associations and confounding variables and interactions were tested in the model. Confounders evaluated were *Giardia* status, IBS, CF, age, sex, marital status and education, and interactions from IBS or CF were tested in the regression model. The results were given as ORs with 95% CI.

In **Paper I** and **Paper II** all analyses were performed using SPSS Statistics for Windows, Version 22, and in **Paper III** SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY).

3.5. Ethical approval

Paper I and **Paper II** were 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). **Paper III** was approved by the Regional Committee for Ethics in Medical Research (ref. no. 2014/1372).

4. Results

4.1. Paper I

In **Paper I** we investigated complications after infection with *Giardia lamblia* on the backdrop of the previously shown associations with IBS and CF, to see if asthma or allergy affected these known associations three years after infection. In the three year follow-up study data was collected by mailed questionnaires to 1252 laboratory confirmed patients with *Giardia* and compared with a matched control group of 3598 individuals. The response rate was 65.3 % (817/1252) among *Giardia* exposed and 31.4 % (1128/3598) among controls.

Table 1: Composition of study groups at the three-year follow-up after the *Giardia* outbreak, Bergen, Norway, 2004.

	Questionnaires sent N	**Study population n**	**Response rate %**
***Giardia* exposed**	1252	817	65.3
Control group 1	2504	862[1]	34.4
Control group 2	1094	271[2]	24.7
Total control group	3598	1128	31.4

[1]) 3 controls removed due to giardiasis in 2004, [2]) 2 controls removed due to giardiasis in 2004

The prevalence of asthma was similar in the groups with 12.2 % (99/809) among *Giardia* exposed compared with 12.1 % (135/1120) among controls (p = n.s.). There was a difference in prevalence of allergy with 28.8 % (231/802) among the *Giardia* exposed compared with 26.1 % (286/1095) among controls ($p < 0.001$). The combination of both asthma and allergy was present in 6.4 % (52/811) of *Giardia* exposed and 5.9 % (66/1121) of controls (p = n.s). As shown in a prior paper from this material, the prevalence of IBS was 46.1 % (355/770) among *Giardia* exposed compared with 14.0 % (155/1106) among controls, and the prevalence of CF was

46.1 (366/794) among *Giardia* exposed compared with 12.0 % (134/1118) among controls (both $p < 0.001$).

Among *Giardia* exposed with asthma the prevalence of IBS was 47.8 % (43/90) compared with 45.3 % (291/642) in *Giardia* exposed without asthma ($p = 0.662$). Among controls with asthma there was a difference between groups with a prevalence of IBS of 23.9 % (32/134) compared with 12.2 % (114/936) among controls without asthma ($p <0.001$). Confounding and interactions were evaluated by logistic regression modeling. Confounders evaluated were sex, age, work, income and level of education. Stratified analyses for asthma and allergy were used to compare the groups of exposed patients and controls given in relative risks (RR). The control group was chosen as the reference group. We found that the RR for IBS among *Giardia* exposed with asthma was 2.03 (95% CI: 1.45, 2.62) compared with controls with asthma. The RR for IBS among *Giardia* exposed without asthma was 3.80 (95% CI: 3.30, 4.32) compared with controls without asthma.

Among *Giardia* exposed with allergy the prevalence of IBS was 45.9 % (100/218) compared with 43.7 % (190/435) in *Giardia* exposed without allergy ($p = 0.595$). Among controls with allergy the prevalence of IBS differed between groups and was 17.3 % (49/283) compared with 12.1 % (86/710) among controls without allergy ($p = 0.031$). Logistic regression analyses showed that the RR for IBS among *Giardia* exposed with allergy was 2.68 (95% CI: 2.10, 3.27) compared with controls with allergy. The RR for IBS among *Giardia* exposed without allergy was 3.73 (95% CI: 3.13, 4.34) compared with controls without allergy.

For CF the same analyses were made as for IBS. Among *Giardia* exposed with asthma the prevalence of CF was 51.5 % (51/99) compared with 44.9 % (295/657) in *Giardia* exposed without asthma ($p = 0.218$). Among controls with asthma we found a significant difference in prevalence of CF of 19.3 % (26/135) compared with 10.7 % (102/949) among controls without asthma ($p = 0.004$). Adjusted analyses showed that the RR for CF among *Giardia* exposed with asthma was 2.73 (95% CI: 1.98, 3.45) compared with controls with asthma.The RR for CF among *Giardia* exposed

without asthma was 4.25 (95% CI: 3.66, 4.85) compared with controls without asthma.

Among *Giardia* exposed with allergy the prevalence of CF was 49.8 % (113/227) compared with 42.9 % (193/450) in *Giardia* exposed without allergy (p = 0.089). Among controls with allergy the prevalence of CF was 13.7 % (39/285) compared with 11.0 % (79/719) among controls without allergy (p = 0.232). Adjusted analyses showed that the RR for CF among *Giardia* exposed with allergy was 3.64 (95% CI: 2.87, 4.42) compared with controls with allergy. The RR for CF among *Giardia* exposed without allergy was 4.00 (95% CI: 3.33, 4.68) compared with controls.

In conclusion, having asthma or allergy did not significantly impact the prevalence of IBS or CF three years after infection with *Giardia lamblia*. In the control group, however, atopy was strongly associated with IBS and CF.

4.2. Paper II

In **Paper II** the aim was to investigate if prior infection with *Giardia lamblia* was associated with changes in sleep, more explicit excessive daytime sleepiness, insomnia and self-reported sleep need. Furthermore, associations to IBS and CF were studied. It was based on the three-year follow-up after infection with *Giardia* described under results in **Paper I**.

Excessive daytime sleepiness was reported by 31.5 % (245/777) of the *Giardia* exposed and 14.1 % (154/1090) of controls ($p < 0.001$). It was measured with the validated Epworth Sleepiness Scale with a max score of 24 and cut-off score for daytime sleepiness of ≥ 11. The mean score among the *Giardia* exposed was 8.5 compared with 6.6 among controls ($p < 0.001$). Among the *Giardia* exposed with IBS, 41.8 % (143/342) had excessive daytime sleepiness compared with 28.2 % (42/149) in the control group with IBS ($p = 0.005$). Among the *Giardia* exposed with CF 50.6 % (175/346) had excessive daytime sleepiness compared with 36.9 % (48/130) in the control group with CF ($p = 0.010$). Logistic regression analyses was performed on excessive daytime sleepiness with scoring ≥ 11 as the outcome. Status (exposed/control), IBS, CF, age, sex, marital status, education, employment status and student status during the outbreak was the exposure and confounding factors. The control group was chosen as the reference group. Adjusted analyses showed an OR of excessive daytime sleepiness of 1.40 (95% CI, 1.06-1.86) for *Giardia* exposed compared with controls.

Insomnia was reported by 15.4 % (125/811) of the *Giardia* exposed and 8.8 % (98/1116) of controls ($p < 0.001$). Among the *Giardia* exposed with IBS, 22.9 % (81/354) had insomnia compared with 17.5 % (27/154) in the control group with IBS ($p = 0.195$). Among the *Giardia* exposed with CF, 26.6 % (97/364) had insomnia compared with 31.1 % (41/132) in the control group with CF ($p = 0.365$). Logistic regression analyses was performed on the outcome of insomnia as described in the previous section on excessive daytime sleepiness. The adjusted OR for insomnia was 0.93 (95% CI, 0.65-1.35) for *Giardia* exposed compared with controls.

Self-reported sleep need was measured in hours with mean sleep need among *Giardia* exposed of 8.0 hours (standard deviation (SD) 1.4) compared with 7.5 hours (SD 1.1) among controls ($p < 0.001$). For participants with IBS, the mean sleep need was 8.2 hours (SD 1.5) among *Giardia* exposed compared with 7.9 hours (SD 1.2) among controls ($p = 0.056$). For participants with CF, the mean sleep need was 8.4 hours (SD 1.5) among *Giardia* exposed compared with 8.1 hours (SD 1.4) among controls ($p = 0.015$). Multiple linear regression analyses were performed on self-reported sleep need with the intercept representing the reference groups as a compilation of the chosen reference in each examined and considered possible associated exposure or factor (status, IBS, CF). The intercept describing the mean sleep need in the control group without IBS and without CF of 6.55 hours ($p < 0.001$). *Giardia* exposure added 0.12 hours (CI, 0.01-0.24) to the sleep need on average, increasing the sleep need by 7 minutes ($p = 0.040$).

No significant effect modification between IBS or CF and the association to exposure status or the three outcomes on sleep was found. In adjusted analyses on each of the sleep outcomes, analyses were also performed on IBS and CF. Adjusted analyses on excessive daytime sleepiness showed an OR of 1.78 (95% CI, 1.34-2.37) for IBS compared with participants without IBS and 4.12 (95% CI, 3.10-5.47) for CF compared with participants without CF, regardless of exposure status. For insomnia adjusted analyses showed an OR of 1.77 (95% CI, 1.24-2.54) for IBS, and 4.75 (95% CI, 3.30-6.84) for CF. And for sleep need having IBS increased the sleep need by 0.27 hours (95% CI, 0.14-0.40) and CF increased the sleep need by 0.78 hours (95 % CI, 0.65-0.92). These analyses disclosed independent and stronger associations between IBS and CF and the outcomes on sleep (excessive daytime sleepiness, insomnia, sleep need) than the associations between exposure status and the measured outcomes.

In conclusion, *Giardia* exposure three years prior was independently associated with excessive daytime sleepiness and increased sleep need, but not with insomnia. IBS and CF were both independently and stronger associated to the sleep outcomes.

4.3. Paper III

Paper III was based on the ten-year follow-up study after the outbreak of *Giardia lamblia* investigating fibromyalgia after infection and possible associations with IBS and CF. The response rate among *Giardia* exposed was 50.3 % (592/1176) and among controls 30.4 % (708/2330).

Table 2: Composition of study groups at the ten-year follow-up after the *Giardia* outbreak, Bergen, Norway, 2004.

	Questionnaires sent **N**	**Study population** **n**	**Response rate** **%**
***Giardia* exposed**	1176	592[1]	50.3
Control group	2330	708[2]	30.4

[1]) 2 questionnaires returned incomplete, [2]) 6 controls removed due to giardiasis in 2004 and 6 questionnaires returned incomplete

The prevalence of fibromyalgia was significantly higher in the *Giardia* exposed group with 8.6 % (49/572) compared with 3.1 % (21/673) in the control group ($p < 0.001$). As shown in a previous paper, the prevalence of IBS ten years after infection was 43.1 % (248/576) among *Giardia* exposed compared with 13.7 % (94/685) among controls, and the prevalence of CF was 26.1 (153/587) among *Giardia* exposed compared with 10.5 % (73/692) among controls (both $p < 0.001$).

We found considerable overlapping between all three conditions; fibromyalgia, IBS and CF. From the perspective of fibromyalgia, 87.0 % (40/46) of the *Giardia* exposed with fibromyalgia also had IBS and 69.4 % had CF (34/49), compared with the controls with fibromyalgia, where 50.0 % (10/20) had IBS and 42.9 % (9/21) had CF (both $p < 0.001$). Among *Giardia* exposed 4.6 % (27/590) had all three conditions compared with 0.4 % (3/696) in the control group ($p < 0.001$).

Looking at IBS, 16.5 % (40/242) of *Giardia* exposed with IBS also had fibromyalgia, compared with 11.2 % (10/89) among controls with IBS ($p < 0.001$). And last looking at CF, 22.8 % (34/149) of *Giardia* exposed with CF also had fibromyalgia, compared with 12.9 % (9/70) among controls with CF ($p < 0.001$).

Logistic regression analyses adjusted for IBS and CF were performed to evaluate the effect of exposure status on the outcome of fibromyalgia. The control group was chosen as the reference group and results given in odds ratios. The unadjusted OR for having fibromyalgia was higher for *Giardia* exposed compared with controls (OR: 2.91, 95% CI: 1.72, 4.91). Adjusting for IBS and CF, this difference was no longer present with an OR of 1.05 (95% CI: 0.57, 1.95). Regardless of exposure status, in participants without CF the OR for fibromyalgia was 6.27 times higher for participants with IBS than for those without (95% CI: 3.31, 11.91). And in participants without IBS the OR for fibromyalgia was 4.80 times higher for those with CF than for those without (95% CI: 2.75, 8.37).

In conclusion, the prevalence of fibromyalgia was higher in the *Giardia* exposed group compared with the control group. We also showed that fibromyalgia was strongly associated with IBS and CF. Since the prevalence of IBS and CF was high in the *Giardia* exposed group, this may account for the difference in prevalence of fibromyalgia between the exposed group and the control group.

5. Discussion

The main findings in this thesis are that acute infection with *Giardia lamblia* is associated with extra-intestinal complications three and ten years later. We found the studied complications to be associated with IBS and CF. Excessive daytime sleepiness and increased sleep need three years after infection was independently associated with giardiasis. Atopy was found to be associated to IBS and CF in the control group three years after infection, whereas among the *Giardia* exposed our study suggest that the effect of atopy on IBS and CF after giardiasis could be concealed by high prevalences of the outcomes. Fibromyalgia was more common among *Giardia* exposed ten years after infection, but this was associated to the high prevalences of IBS and CF.

5.1. Methodological considerations

5.1.1. Study design

The design of this study was a controlled cohort study with the starting point being the *Giardia* outbreak in 2004. Data were collected three, six and ten years after the outbreak. In **Paper I** the study was described as a historic cohort study, in **Paper II** as a cohort study, whereas in **Paper III** the term prospective cohort study was used. This distinction has been up for continuous discussion within the research group and is a known source of confusion in epidemiologic studies. A cohort study is a longitudinal study where participants are included at a specific time point and grouped based on presence or absence of exposure to a specific factor, in our case *Giardia* infection in 2004, and followed for a period to detect development of disease. Cohort studies are divided into retrospective or historic cohort studies and prospective cohort studies.

The difference between these terms is not straightforward and the terms are used inconsistently (140). One definition describes cohort studies as prospective and case-control studies as retrospective. This only refers to design label and does not give any information on the actual study design. A more thorough description refers to when the follow-up of subjects has happened, before the initiation of the study of after.

When the person-time, i.e., the time participants contributed to a study, is accumulated after the study is conducted it is called prospective. A third definition refers to which order the recording of exposure and occurrence of disease happens. If occurrence of disease has happened at the time of collecting information about exposure this could influence the results by recall bias. In our study we report prevalent cases and not incident cases after the exposure. Information could therefore have been collected after occurrence of diseases of interest and the collected information could be affected by the exposure diagnosis. We cannot say if the outcomes of interest had developed before time of measurement as we do not have baseline data or information prior to the outbreak. Some of the cases had or were most likely eligible for the outcome diagnoses at baseline in both groups.

Studies can be both retrospective and prospective, and this is the case for our study and contributes to confusion regarding these definitions. During the outbreak in 2004 a biobank of patients with positive fecal test for *Giardia lamblia* was set up. In 2006 they were contacted for inclusion in the planned cohort study, and the control group were included in 2007 for the three-year follow-up. In this respect our three-year follow-up study can be referred to as retrospective as it involves past occurrences and the *Giardia* exposed subjects were not actually followed from time of exposure. After the three-year follow-up our study onward followed the patients and controls up to ten years making a prospective cohort study a more precise description of this part of the study.

5.1.2. Precision

Inaccuracy that occur due to random error affects the precision of an estimate (141). The precision of a measure is evident from the confidence interval, with a wider interval portraying a less precise estimate, and strength of association. Random error occurs because results in a study are based on a sample from the population, which may not reflect the general population. Methods to reduce random error is including a large study population, using several questions to increase internal validity and using validated tools.

Our study had many participants at every follow-up, the study population was still declining at each measuring point. In the three-year follow-up the response rate in the control group was 34.4 % (862/2504) and it was decided to expand the control group to hopefully increase the response rate. In the additional control group, the response rate was 24.7 % (271/1094) and thereby further reducing our total response rate among controls to 31.4 % (1128/3598). We ended up with a larger number of cases, which might have had an impact on random error, but the total response rate was reduced, increasing the risk of systematic error (see below). Also, in stratified analyses some groups became very small resulting in wider confidence intervals and lower precision.

Validated questionnaires were used for IBS, CF, excessive daytime sleepiness and fibromyalgia which is beneficial for precision.

5.1.3. Validity

Systematic error are errors in estimates that differ from the truth and is not dependent on sample size (141). Systematic error impact the validity in a study. Important sources for systematic error are different kinds of bias and confounding.

5.1.3.1. Selection bias

Selection bias arise when factors influence how participants are selected to a study and factors that influence study participation (140, 141). This type of bias is less likely in a prospective cohort study since the exposure comes prior to likely development of the outcomes. Still, there are some challenges of selection bias in our study. Exposed individuals were identified based on a positive fecal test for *Giardia lamblia*, and this was influenced by patient's health care seeking behaviour and how they were managed. We do not know how many of patients with symptoms that contacted the health care services, how many were well when the outbreak was detected, who were tested or not, and the number of stool samples that were submitted for each patient. A patient with a classic gastroenteritis during the outbreak was possibly treated without testing because of the high likelihood of *Giardia* being the cause, whereas less ill or less typical presentations of *Giardia* might be more

frequently tested due to insecurity in diagnosis and become a bigger part of the exposed group because testing was applied. Since being tested for *Giardia* during the outbreak was dependent on the patient seeking medical care and the submission of a stool sample the selection could be biased based on health care seeking behavior and how the physicians investigated symptoms.

Loss to follow-up is another possible cause of selection bias as participants with symptoms or symptoms asked for in the questionnaires could be more inclined to participate in the study. Whereas participants without symptoms might feel that the questions asked after the outbreak did not concern them or they may have lost interest in participating in such a study as time went by. Furthermore, one cannot ignore the possibility that the patients with the worst complications did not have the energy to complete the questionnaire or participate in the study.

5.1.3.2. Information bias

Systematic errors in data collection from a study population leads to information bias (141). Information bias and its direction depend on if the errors of the exposure or outcomes depend on the specific value of the variable, the specific values of other variables or errors in measurement of other variables (140). E.g., participants who are truly exposed may be classified as nonexposed and vice versa, and likewise with outcome variables. Errors in categorization is called misclassification.

In our study misclassification into the *Giardia* exposed group was less likely as this group consisted of individuals with positive fecal test for *Giardia*. The possibility of misclassification would be dependent on the sensitivity and specificity of the test. A high specificity is particularly important because this describes the degree of certainty to classify someone without disease as healthy and thereby reduce the probability of a false positive test result, in our case falsely shown *Giardia lamblia* in a fecal test. Sensitivity describes how good a test is when it comes to detect a disease in someone who actually has the studied disease, and thereby with a high sensitivity the less probability of a false negative test result. In our study, a falsely negative result would exclude a participant, whereas a falsely positive result would include a participant

without the mandatory exposure, *Giardia* infection during the outbreak, and become part of the follow-up study with possible impact on results.

The risk of misclassification is higher in the control group. They were chosen from the same municipality as the outbreak occurred, and we cannot rule out that some were infected during the outbreak. *Giardia* infection can be asymptomatic, and testing during the outbreak to rule out infection in asymptomatic individuals because of possible contact with contaminated water were not performed. In addition, the inclusion in the control group was relying on the individual disclaiming *Giardia* infection during the outbreak. We tried to reduce this by asking whether the controls had giardiasis during the outbreak, and whether this was confirmed by a physician. Controls with physician-confirmed giardiasis were excluded from the study.

Recall bias is a kind of information bias that is particularly problematic in retrospective studies when participants give information about factors in the past. This is not a great concern in our study where we asked about current symptoms.

The *Giardia* outbreak received massive media attention with patients expressing their concerns and health issues and inflicted political pressure for the municipality of Bergen to claim responsibility for the outbreak. Full responsibility was accepted, and compensation given to affected individuals in 2005. With this backdrop, another type of bias might have been introduced: *Association bias* or a type of *confirmation bias*, in lack of a more precise term. We cannot ignore that *Giardia* during the outbreak might alter the way the participants responded to the questionnaires thinking or wanting this exposure to be an explanation of the health issues they experienced later. The *Giardia* exposed could report more complaints as they might be more aware of symptoms after the infection and be more concerned with symptoms being abnormal. Also, if they had present symptoms as was focused on in the questionnaires at time of measurement, they might exaggerate the symptoms because this study is focusing on an infection they know they were exposed to, and they might be inclined to attribute their health issues to this event.

5.1.3.3. Confounding

Confounding is an important concept in observational studies and occurs when an association between an exposure and an outcome is confused by the effect of another factor, it is a true but misleading association (141). The observed association can partly or totally be caused by the effect of the confounder. Matching is a way to control confounding where potential confounders are equally distributed among the comparing groups. This was done in our study by matching controls to *Giardia* exposed individuals on age and sex in a 2:1 proportion. Somewhat low response rates make this control for confounders likely to be less successful.

Confounding can also be controlled for in analyses by stratification or choice of statistical methods. Stratification is a method where the strength of association is separately shown for each strata or level of the factor evaluated. In our studies we used logistic regression modelling to control for factors evaluated as possible confounders, such as age, sex, work, income, marital status, level of education, exposure status, IBS and CF.

5.2. Interpretation

In this thesis, we found that infection with *Giardia lamblia* is associated with long-term extra-intestinal complications. These are in turn strongly associated with concurrent IBS and CF. We have demonstrated that atopy was strongly associated with IBS and CF in a population not exposed to *Giardia,* but high prevalences of these disorders among the *Giardia* exposed population might disguise a possible effect that atopy may have in this group as well. Post-infectious sleep disturbances were found three years after infection and associations to IBS and CF are shown. A high prevalence of fibromyalgia was found among *Giardia* exposed ten years after *Giardia* infection. Fibromyalgia was strongly associated with IBS and CF, which could explain the difference in prevalence of fibromyalgia among the *Giardia* exposed compared with controls as these disorders were more common in the

exposed group and fibromyalgia was not directly associated to prior *Giardia* infection.

5.2.1. Can cause-effect explain some of our findings?

Observational studies are not designed to prove causality but may contribute to inform this question based on the presence of certain criteria. Cause-effect relationship can and should still be discussed in relation to strength of association, biologic credibility, consistency with previous literature, time sequence and dose-response relationship which are all considered criteria for this assessment (141).

Strength of association and consistency with other investigations

Strength in an epidemiological study can be considered by the magnitude of the observed association, with a stronger association making causality more likely. A weak association cannot be ignored as causality is still possible. Confounding must also be considered. In our study on atopy, we investigated whether asthma or allergy had an impact on the already established association to IBS and CF after infection with *Giardia lamblia* (19). Other studies demonstrate results consistent with our findings on IBS and CF after infections (129, 142).There was a high prevalence of IBS and CF among the *Giardia* exposed compared with controls. In adjusted analyses, having atopy did not affect the prevalence of IBS or CF among the *Giardia* exposed. However, in controls having asthma or allergy clearly affected the outcomes. Atopy seems to impact the development of IBS and CF in subjects not exposed to giardiasis, but we cannot ignore the high prevalences of IBS and CF among the *Giardia* exposed. When we have outcomes in magnitudes close to 50 %, one can imagine this level of outcome to be “saturated” to its maximum capacity and thus conceal the difference seen among controls. Among controls with and without atopy there is a clear difference that supports a strong association between atopy and the outcomes. IBS in relation to atopy has previously been suggested and demonstrated, whereas CF is less studied, but has also been shown in association to atopy (39, 143, 144).

Sleep disturbances and prior infection with *Giardia* was independently associated, but IBS and CF also had an impact on this relationship. For excessive daytime sleepiness and increased sleep need it was a stronger association to IBS and CF, than *Giardia* infection. Whereas for insomnia there was no independent association to *Giardia* infection, so the increase in this condition was associated to IBS and CF which is highly present among the *Giardia* exposed group and could therefore explain this higher prevalence of insomnia in this group. There are limited findings in the literature on associations between infections and sleep disturbances, and none on giardiasis to support our results (52-54). Associations between sleep disturbances and IBS and CF/CFS are previously studied (64, 145). Difficulties in interpreting and separating sleep disorders from fatigue makes this association more challenging to explain and confirm.

Similar results were also present in studying fibromyalgia ten years after *Giardia* infection. There was a higher prevalence of fibromyalgia among the *Giardia* exposed group, but this difference disappeared in adjusted analyses, as fibromyalgia seems to be dependent on IBS and CF. Among the *Giardia* exposed there was a high prevalence of IBS and CF, and the increased prevalence of fibromyalgia can be attributed to this. Overlap between fibromyalgia, IBS and CF is well-known (83, 84). Why and how these conditions overlap is unclear, but they do have overlapping symptoms and criteria for diagnosis. A cause-effect relationship between giardiasis and IBS or CF is likely, but based on our findings this is not the case with fibromyalgia which seems to be associated with these conditions as a secondary reaction or response in the body or the immune system.

Our study show strong associations between *Giardia* infection and IBS, CF, and sleep disturbances, but also associations between IBS and CF to atopy and fibromyalgia. Based on relatively high RRs and ORs these associations may be considered strong. Also, probable confounders were adjusted for in analyses. Covariations of conditions are the most likely and undeniable explanation, but the magnitude of associations are of convincing proportions so causality based on strength of associations cannot completely be ruled out and should be assessed as a possibility. Lack of similar

studies and data in the literature makes the research of consistency challenging regarding causality. In the future we might have more data to support such a relationship and more understanding of what *Giardia* infection can lead to, but for now we must acknowledge the uncertainty discussed above when carefully examining these potential relations.

Biologic credibility

There are limited findings in the literature on *Giardia lamblia* for comparisons with our study and to support our results. Possible immunologic explanations for post-infectious IBS and CF have been explored on sample populations from the *Giardia* study suggesting an immunological abnormality in these patients (146, 147). *Giardia* as a pathogen for long-term complications is not largely investigated or understood. Studies suggest a wide variety of post-infectious complications from acute gastrointestinal infections (148). From what we know today our findings are plausible, but time will tell if today's understanding holds up with further research and understanding of these conditions.

Time sequence and dose-response relationship

The three criteria above are the strongest criteria to consider causality in a study, but time sequence and dose-response relationship are also often considered.

From what we know biologically and physiologically to be probable, an appropriate time sequence of the association with exposure being prior to the outcomes is needed. In a prospective cohort study such as ours we can postulate this as we have defined *Giardia* exposure at a certain time and followed the patients onward as our outcomes reveal itself. Still, we do not have baseline data or data prior to the outbreak so we cannot say what developed after the infection and what was there beforehand. These conditions are more common with higher age, so as our population ages more will presumably experience these conditions, which will also account for some of our findings. Still, the difference in prevalence of the outcomes between our groups are larger than aging or chance alone are likely to explain.

A dose-response relationship is difficult to consider in an infection-study as we do not have any measure of the "amount of *Giardia* exposure" the exposed participants experienced. We also cannot say if the patients with more long-term symptoms were more ill during the outbreak, whether those included in the study were the most ill patients and therefore subjects performing fecal testing, if those with a positive test were those with most cysts in stools or if actual number of cysts would impact the development of long-term complications. A dose-response relationship could be present and masked by lack of knowledge and a way of measuring this, or it could not be the case in giardiasis at all.

5.2.2. MUPS – can we generalize our findings?

In the discussion about MUPS fibromyalgia, IBS and CF are held up as typical disorders under this umbrella, and there is overlap in the prevalence of all these conditions (83, 84). Other conditions considered part of MUPS include temporomandibular disorder, multiple chemical sensitivity, tension headache, interstitial cystitis, globus syndrome, premenstrual syndrome and post-concussion syndrome, among others (83, 149). An ongoing discussion in this field is whether it is right to assemble them under the same diagnosis or if they are different entities.

The MUPS diagnosis is made from criteria that highly overlap, trying to describe disorders that also have similar presentations, but from different organ systems (83). For example, the criteria for fibromyalgia include questions on fatigue, achievement of rest after sleep and abdominal pain, which are all symptoms part of other disorders. There are not consistent pathological findings in investigations of MUPS symptoms. There is no natural division of the diagnoses and the different disorders under the term are based on our present understanding of these complex conditions. Different approaches in understanding these conditions have been suggested with central sensitization, dysfunction of the central nervous system, trauma, psychological distress and psychiatric disorders without safe conclusions to explain how they possibly cause the different conditions or to what extent they contribute to development of such symptoms (83, 150). Every explanatory model suggested are

limited by the fact that they cannot embrace the occurrence of unexplained symptoms in a large proportion of patients. From a physiological and biological perspective, there are likely interindividual differences that can cause more and several symptoms in some and display itself more frequently from some organ systems. Also, it has been suggested that the most prominent symptoms lead to investigations within a medical specialty causing a patient to receive a MUPS diagnosis closest to that specialty, and not necessarily a diagnosis based on the patient's total symptomatology (149).

By assembling the different diagnoses under one term, MUPS, it is difficult to find the distinct differences between the disorders or patients affected by the different conditions. Still, the conditions highly overlap and studying this from a perspective of different presentations of similar entities might give helpful insights giving us a better understanding of these disorders contributing to improved care for affected patients.

In our study, we investigated whether infection with *Giardia lamblia* could give extraintestinal complications. MUPS was not our main outcome, but all papers included outcomes of disorders with limited or no objective pathological findings. Sleep disturbances, abdominal symptoms, fatigue and bodily pain are all shown as post-giardiasis symptoms. Asthma was shown among unexposed individuals to be associated with IBS and fatigue. We did show that post-infectious complications after *Giardia* include a variety of symptoms from different organ systems with convincingly high prevalences in the exposed group compared with controls.

Our study imply that various post-infectious symptoms can arise after giardiasis. The mindset of discussions on MUPS, which force us to look at symptoms and previously understandings of disorders in continuously new ways, can be applied for our studies where there are limited prior investigations and knowledge to lean on. We investigated a gastrointestinal infection that gives prolonged gastrointestinal symptoms, but also symptoms not related to the gut. *Giardia* affects the upper small intestine, but a strong association to IBS is shown which has symptoms originating from the middle to lower gastrointestinal tract. Asthma and allergy are found to

increase risk of IBS and CF, even though these conditions are considered related to the respiratory tract. Among other complications associated with giardiasis we find sleep disturbances and chronic fatigue, which are often managed by neurologists. Fibromyalgia, which was found associated to IBS and CF, is considered a rheumatologic disorder. From our studies associations are shown to go in both directions and not just via the precipitating infection. *Giardia* infection can be seen as one of many potential risk factors for a wide variety of symptoms, not just related to where symptoms first turn up or the logically affected organ system from our prior knowledge.

6. Conclusion

In this thesis, we found that infection with *Giardia lamblia* is associated with long-term extra-intestinal complications three and ten years after infection. These complications are in turn strongly associated with concurrent IBS and CF.

Associations found in our studies are strong and reliable, also in light of discussed limitations, showing that post-infectious complications can present itself in many different forms. Limitations to our studies are addressed in this thesis and questions on causality discussed, with the knowledge that observational studies are not designed to prove causality.

The aftermath from a seemingly limited and harmless infection can potentially be more serious than previously anticipated.

7. Further research

There are still unanswered queries concerning long-term and extraintestinal complications after infection with *Giardia lamblia*. Some suggestions for further reseach based on this thesis may be:

We found that atopy did not affect the outcome of IBS or CF among *Giardia* exposed, but in the control group the risk of IBS or CF was strongly associated with atopy. Further reseach on atopy as a possible trigger or mediator for other disorders and the association to IBS and CF should be considered.

We found a high prevalence of fibromyalgia ten years after giardiasis, but this was dependent on IBS and CF. In research on fibromyalgia a lot is still unknown, and we did not have incident cases in our study. In later infectious outbreaks, data on the prevalence of possible post-infectious outcomes like fibromyalgia, IBS and fatigue at baseline in a longitudinal study could contribute to the understanding of development and associations of medically unexplained physical symptoms to infectious agents.

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PAPERS 1-3

PAPER 2

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Excessive daytime sleepiness, sleep need and insomnia 3 years after *Giardia* infection: a cohort study

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ABSTRACT

Objective: To investigate whether prior infection with *Giardia lamblia* is associated with excessive daytime sleepiness, insomnia, and level of sleep need.
Design: A questionnaire was sent to all confirmed cases of giardiasis 3 years after the outbreak and a control group matched on age and gender. Associations were evaluated by use of multiple regression analysis.
Results: Excessive daytime sleepiness (score ≥ 11 on the Epworth Sleepiness Scale) was reported by 31.5% of the *Giardia*-exposed and 14.1% of the controls. In multivariate analysis, excessive daytime sleepiness was independently associated with *Giardia* exposure, with an adjusted odds ratio of 1.40 (95% confidence interval [CI], 1.06-1.86). Insomnia was reported by 15.4% of *Giardia*-exposed and 8.8% of controls, adjusted odds ratio was 0.93 (95% CI, 0.65-1.35). Mean (SD) self-reported sleep need was 8 (1.4) hours among *Giardia*-exposed and 7.5 (1.1) hours in the control group ($P < .001$). The adjusted regression coefficient was 0.12 (95% CI, 0.01–0.24).
Conclusion: Being exposed to *Giardia* was independently associated with excessive daytime sleepiness and larger sleep need, but not with insomnia.

Introduction

It is commonly believed that infections may interfere with sleep patterns. Some infections have been associated with sleep disorders, and a change in sleep pattern has been shown for streptococcal infection, Epstein-Barr infection and HIV.[1–3] Some of these infections are also associated with chronic fatigue syndrome (CFS).[4,5]

In 2004, there was an epidemic of giardiasis in the city of Bergen, Norway, and it has been estimated that 2500 inhabitants received treatment.[6] Our group has previously reported a high prevalence and relative risk of irritable bowel syndrome (IBS) and chronic fatigue (CF) in giardiasis patients as compared with a control group 3 and 6 years after the outbreak.[7,8] We have not found any studies investigating a possible connection between *Giardia* infection and sleep disorders.

The relationship between fatigue and sleepiness is not entirely clear. Sleepiness deals with the probability of actually falling asleep, whereas one can be fatigued without being sleepy, for instance, after strenuous exercise. It has previously been shown that patients with CFS are both more fatigued and sleepier than a healthy control group, but only more fatigued than a group with excessive daytime sleepiness.[9] In addition to sleepiness and fatigue, insomnia symptoms and self-reported sleep need may be changed after severe infection.

Against this backdrop, we explored the association between sleep problems and sleepiness as outcomes with a specific infectious agent as the risk factor. The aim of the study was to compare the prevalence of excessive daytime sleepiness, insomnia, and self-reported sleep need 3 years after *Giardia* infection with a matched control group. We also analyzed how these outcomes were related to CF and IBS.

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Methods

The study was developed as a cohort study. Data acquisition was performed by mailed questionnaires 3 years after the outbreak to all 1252 patients who had a positive fecal test result for *Giardia lamblia* during the outbreak and a control group of 3598 individuals. The population hit by the outbreak was younger and had a higher proportion of females compared with the general population.[6] Consequently, the control group was randomly sampled with 2 persons with the same age and gender from the entire population in Bergen, thus establishing a 2:1 matched control cohort. The control group was selected by the help of Statistics Norway.

Questionnaires were sent to participants by regular mail in October 2007, and nonrespondents were mailed again after 1 month. In an effort to reduce possible bias caused by a low response rate among controls, this group was expanded by adding 2 more controls for each exposed individual when none of the first 2 controls had responded. As a result, the questionnaire was mailed to 1094 additional controls in May 2008.[7]

Detected *G lamblia* in stool samples during the outbreak in 2004 was the exposure in this study. We had 3 main outcome variables. The first was daytime sleepiness measured by the Epworth Sleepiness Scale (ESS) 3 years after *Giardia* exposure.[10] ESS evaluates subjective sleepiness and consists of 8 questions. Each question describes different situations and the participant is asked to rate their probability to doze off or fall asleep on a 4-point Likert scale where the responses are assigned values from 0 to 3. The responses are added to give the total ESS score, which indicates the level of sleepiness that the participant experiences. The maximum score is 24, and a value of ≥11 is classified as excessive daytime sleepiness.[10,11] Where there was a missing value on any of the 8 questions, the ESS was deemed invalid. The Norwegian version of this scale has been validated.[11] The second outcome variable was insomnia measured by the question "During the last month, how often have you experienced insomnia?" This question had 4 options ranging from "never or seldom," "1-2 times per month," "about once a week," and "more than once a week." "More than once a week" was classified as having insomnia, and this outcome was analyzed as a dichotomous variable. The third outcome variable was self-reported sleep need measured by the question "How much sleep do you need to feel rested?" where the participants could fill in the number of hours they needed to sleep.

CF was defined by the response to the Fatigue Questionnaire (FQ) developed by Chalder et al.[12] The FQ consists of 11 questions measuring both physical and mental fatigue and has previously been used in its translated form in a study on fatigue in the general Norwegian population.[13] CF was defined as a dichotomised score of 4 or more, given that the participant had experienced fatigue for the last 6 months. IBS was defined according to the Rome III diagnostic criteria for functional gastrointestinal disorders[12,14] as abdominal pain or discomfort of certain regularity linked to alterations in bowel movements, also described in a previous article from this study.[7]

Statistical analyses

The χ^2 test was applied to test differences between proportions. *T*-test was applied to compare means. Results were adjusted for IBS, CF, age, gender, marital status, education, employment status, and student status in 2004. Logistic regression analysis was used to investigate the association between excessive daytime sleepiness (ESS score ≥ 11) and *Giardia* exposure, and between insomnia and *Giardia* exposure. The results are reported as odds ratio (OR) and confidence interval (CI). Multiple linear regression analysis was applied to self-reported sleep need (in hours) to study main effects from and interactions between *Giardia* status and the presence of IBS and CF. Interaction was tested using interaction terms. Regression was also used to estimate differences in mean and SD between the groups. All analyses were performed in SPSS version 22.

Ethical approval

This study 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).

Results

The overall response rate was 40.1% (1945/4850), with a 65.3% (817/1252) response rate among exposed and 31.4% (1128/3598) among controls. Characteristics of the exposed group and controls are shown in Table 1. The ESS was incomplete in 78 cases. In addition, 18 cases had missing value on insomnia, and 30 cases on sleep need. There were missing data on IBS and CF in 70 and 33 cases, respectively.

Excessive daytime sleepiness was reported by 31.5% of *Giardia*-exposed (245/777) and 14.1% of controls (154/1090; $P < .001$). The mean ESS score in the *Giardia*-exposed group was 8.5 compared with 6.6 in the control group ($P < .001$). Among the *Giardia*-exposed with IBS, 41.8% (143/342) had excessive daytime sleepiness as compared with 28.2% (42/149) in the control group with IBS ($P = .005$). Among the *Giardia*-exposed with CF, 50.6% (175/346) had excessive daytime sleepiness as compared with 36.9% (48/130) in the control group with CF ($P = .010$; Table 2).

Insomnia was reported by 15.4% of *Giardia*-exposed (125/811) and 8.8% of controls (98/1116; $P < .001$). Among the *Giardia*-exposed with IBS, 22.9% (81/354) had insomnia as compared with 17.5% (27/154) in the control group with IBS ($P = .195$). Among the *Giardia*-exposed with CF, 26.6% (97/364) had insomnia as compared with 31.1% (41/132) in the control group with CF ($P = .365$; Table 3).

Self-reported sleep need was reported to a mean (SD) of 8.0 (1.4) hours in the *Giardia*-exposed and 7.5 (1.1) hours in the control group

Table 1
Characteristics of patients with verified *Giardia* infection during an outbreak in 2004 and a control group who did not contract the infection.

Characteristics	*Giardia* group (n = 817)		Control group (n = 1128)		*P*
Female, n (%)	540	(66.1)	738	(65.4)	.759[a]
Age (y), mean (range)	36.0	(4-94)	36.3	(4-89)	.667[b]
Age groups, n (%)					
Age 0-19 y	39	(4.8)	36	(3.2)	.108[a]
Age 20-39 y	526	(64.4)	736	(65.2)	
Age 40-59 y	187	(22.9)	276	(24.5)	
Age 60-79 y	56	(6.9)	76	(6.7)	
Age 80-99 y	9	(1.1)	4	(0.4)	
Marital status, n (%)					
Single	271	(33.5)	293	(26.1)	.004[a]
Married	497	(61.4)	778	(69.3)	
Divorced	33	(4.1)	41	(3.7)	
Widowed	9	(1.1)	11	(1.0)	
Education (highest level), n (%)					
Primary school	37	(4.7)	59	(5.3)	.004[a]
Secondary school	169	(21.3)	308	(27.7)	
University	587	(74.0)	746	(67.0)	
Main employment status, n (%)					
Worker	576	(71.1)	881	(78.7)	<.001[a]
Student	137	(16.9)	121	(10.8)	
Unemployed/retired	70	(8.6)	96	(8.6)	
Other	27	(3.3)	22	(2.0)	
Student during the outbreak, n (%)	299	(37.3)	269	(24.2)	<.001[a]

Exposed and controls were matched by gender and age.
[a] Pearson χ^2 test from $2 \times k$ table.
[b] Gosset *t* test for independent samples.

Table 2
Prevalence of excessive daytime sleepiness (ESS score ≥ 11) among *Giardia* exp and age- and gender-matched controls according to the presence of IBS and CF, or any combination of the two, 3 years after a *Giardia* outbreak in 2004 in Bergen, Norway.

		No. of *Giardia* exp/ No. of controls[a]	Excessive daytime sleepiness				P[b]
			Giardia exp		Controls		
			n	%	n	%	
Total		777/1090	245	31.5	154	14.1	<.001
IBS	Yes	342/149	143	41.8	42	28.2	.005
	No	392/922	86	21.9	110	11.9	<.001
CF	Yes	346/130	175	50.6	48	36.9	.010
	No	412/954	63	15.3	105	11.0	.031
IBS/CF	Both	208/47	112	53.8	20	42.6	.196
	None	273/837	35	12.8	82	9.8	.173
	IBS and no CF	125/100	27	21.6	21	21.0	1.000
	CF and no IBS	115/83	49	42.1	28	33.7	.238

Abbreviations: ESS, Epworth Sleepiness Scale; exp, exposed; CF, chronic fatigue; IBS, irritable bowel syndrome.
[a] Due to missing data, the numbers do not add up to the total number of participants.
[b] P value from exact χ^2 test on comparisons between the *Giardia*-exposed and controls.

($P < .001$). Among the *Giardia*-exposed with IBS, the mean (SD) sleep need was 8.2 (1.5) hours as compared with 7.9 (1.2) hours in the control group with IBS ($P = .056$). Among the *Giardia*-exposed with CF, the mean (SD) sleep need was 8.4 (1.5) as compared with 8.1 (1.4) in the control group with CF ($P = .015$; Table 4).

We tested effect modification of each of IBS and CF on the association between *Giardia* status (exposed/control) and the 3 sleep outcomes (excessive daytime sleepiness, insomnia, and sleep need). No significant effect modification was found.

Table 5 shows results from logistic regression with ESS score ≥11 as the outcome, with *Giardia* status (exposed/controls), IBS, CF, age, gender, marital status, education, employment status, and student status in 2004 as exposures and confounding factors. The adjusted OR was 1.40 (95% CI, 1.06-1.86) for the *Giardia*-exposed as compared with controls. The corresponding adjusted OR was 1.78 (95% CI, 1.34-2.37) for IBS and 4.12 (95% CI, 3.10-5.47) for CF.

Table 6 shows results from corresponding logistic regression analyses of insomnia. The adjusted OR was 0.93 (95% CI, 0.65-1.35) for *Giardia*-exposed as compared with controls. The adjusted OR was 1.77 (95% CI, 1.24-2.54) for IBS, and the adjusted OR was 4.75 (95% CI, 3.30-6.84) for CF.

Table 3
Prevalence of insomnia among the *Giardia*-exposed and age- and gender-matched controls according to the presence of IBS and CF, or any combination of the two, 3 years after a *Giardia* outbreak in 2004 in Bergen, Norway.

		No. of *Giardia*-exposed/ No. of controls[a]	Insomnia				P[b]
			Giardia exposed		Controls		
			n	%	n	%	
Total		811/1116	125	15.4	98	8.8	<.001
IBS	Yes	354/154	81	22.9	27	17.5	.195
	No	413/941	39	9.4	68	7.2	.189
CF	Yes	364/132	97	26.6	41	31.1	.365
	No	426/976	26	6.1	57	5.8	.902
IBS/CF	Both	215/49	67	31.2	18	36.7	.499
	None	283/855	14	4.6	45	5.5	1.000
	IBS and no CF	129/103	12	9.3	9	8.7	1.000
	CF and no IBS	125/83	25	20.0	23	27.7	.240

Abbreviations: IBS, irritable bowel syndrome; CF, chronic fatigue.
[a] Due to missing data, the numbers do not add up to the total number of participants.
[b] P value from exact χ^2 test on comparisons between *Giardia*-exposed and controls.

Table 4
Descriptive statistics for self-reported sleep need for 817 *Giardia* exposed and 1128 controls in Bergen, Norway, 2004 according to the presence of IBS and CF.

		Self-reported sleep need (h)						
		Giardia exposed			Control group			P[a]
		n	Mean	SD	n	Mean	SD	
Total		805	8.0	1.4	1110	7.5	1.1	<.001
IBS	Yes	348	8.2	1.5	151	7.9	1.2	.056
	No	413	7.8	1.3	938	7.4	1.1	<.001
CF	Yes	358	8.4	1.5	130	8.1	1.4	.015
	No	425	7.6	1.1	971	7.4	1.0	.001
IBS/CF	Both	210	8.6	1.5	47	8.4	1.6	.363
	None	283	7.6	1.1	852	7.3	1.0	<.001
	IBS and no CF	128	7.6	1.0	102	7.7	1.0	.471
	CF and no IBS	124	8.3	1.5	83	7.9	1.3	.073

Abbreviations: IBS, irritable bowel syndrome; CF, chronic fatigue.
[a] P value from t test on comparisons between *Giardia* exposed and controls.

Table 7 shows results from multiple linear regression of self-reported sleep need on IBS and CF for *Giardia*-exposed and controls. Also, it is adjusted for age, gender, marital status, education, employment status, and student status in 2004. The intercept of 6.55 shows the mean amount of sleep need in the control group without IBS and CF. Being exposed to *Giardia* added 0.12 hours to the intercept ($P = .040$), having IBS adds 0.27 hours ($P < .001$) and CF adds 0.78 hours ($P < .001$). Adjusted for IBS, CF, age, gender, marital status, education, employment status, and student status in 2004, *Giardia* exposure significantly increased the sleep need with 0.12 hours (ie, 7 min) on average.

Discussion

The main result of this study was that excessive daytime sleepiness and self-reported sleep need were independently associated with acute giardiasis 3 years earlier, but insomnia was not. In this study, the *Giardia*-exposed had a prevalence of excessive daytime sleepiness that was more than twice the prevalence in the control group. In multivariate analyses, the effect of *Giardia* exposure was significant but weak, whereas there was a strong association with CF and an intermediate association with IBS. Insomnia was also associated with IBS and CF, but when adjusting for this in the multivariate analysis, the observed difference between the *Giardia*-exposed and the control group was not significant. This shows that although insomnia was more common in *Giardia*-exposed individuals, the increase in insomnia prevalence was related to the presence of CF and/or IBS. The *Giardia*-exposed had a significantly higher self-reported sleep need than did the control group, and the *Giardia*-

Table 5
Results from logistic regression of excessive daytime sleepiness (ESS score ≥ 11), according to the presence of IBS, CF, and *Giardia* exposure for 817 exposed and 1128 controls in the *Giardia* epidemic in Bergen, Norway, 2004.

	Excessive daytime sleepiness					
	Unadjusted OR	95% CI	P	Adjusted OR[a]	95% CI	P
Control group	1	Reference		1	Reference	
Giardia exposed	2.80	2.23-3.52	<.001	1.40	1.06-1.86	.020
No IBS	1	Reference		1	Reference	
IBS	3.45	2.72-4.37	<.001	1.78	1.34-2.37	<.001
No CF	1	Reference		1	Reference	
CF	6.29	4.94-8.01	<.001	4.12	3.10-5.47	<.001

Abbreviations: ESS, Epworth Sleepiness Scale; OR, odds ratio; CI, confidence interval; IBS, irritable bowel syndrome; CF, chronic fatigue.
[a] Adjusted for IBS, CF, age, gender, marital status, education, employment status, and student status in 2004.

Table 6
Results from logistic regression of insomnia according to the presence of IBS, CF, and *Giardia* exposure for 817 exposed and 1128 controls in the *Giardia* epidemic in Bergen, Norway, 2004.

	Insomnia					
	Unadjusted OR	95% CI	*P*	Adjusted OR[a]	95% CI	*P*
Control group	1	Reference		1	Reference	
Giardia-exposed	1.89	1.43-2.51	<.001	0.93	0.65-1.35	.720
No IBS	1	Reference		1	Reference	
IBS	3.15	2.36-4.21	<.001	1.77	1.24-2.54	.002
No CF	1	Reference		1	Reference	
CF	6.13	4.56-8.24	<.001	4.75	3.30-6.84	<.001

Abbreviations: OR, odds ratio; CI, confidence interval; IBS, irritable bowel syndrome; CF, chronic fatigue.
[a] Adjusted for IBS, CF, age, gender, marital status, education, employment status, and student status in 2004.

exposed with IBS and CF had higher sleep need than did the control groups with IBS (trend) and CF, respectively. In multivariate analyses, *Giardia* exposure was significantly associated with sleep need, but to a lesser degree than IBS and particularly CF.

The research after the outbreak in Bergen has increased our knowledge about the long-term effects of *G lamblia*. The outcomes in this study were chosen after clinicians reported that patients struggled with fatigue, sleep problems, and bowel symptoms long after the actual infection was cured. No former studies have investigated the relationship between sleep and giardiasis. Our study is based on a large outbreak giving statistical power to the results. All participants classified as the *Giardia*-exposed had a positive fecal test result for *G lamblia* during the outbreak in 2004, making misclassification close to impossible. The control group was matched to the *Giardia*-exposed by age and gender, with 2 controls per exposed individual. It is unlikely that any controls have been exposed to giardiasis. *G lamblia* is very rare in Norway, and participants in the control group were asked whether they had been diagnosed with it previously. There is the possibility that some could have been exposed to giardiasis at some point without it being diagnosed, but that would be an exception and not considered to affect the results of this study.

A problem common in questionnaire-based studies is low response rate, and this is also an issue in the present study. Particularly, the response rate was low in the control group, who may not feel the questions concerned them. This gives concerns about selection bias. However, the control group is comparable to the general Norwegian population with respect to sleepiness, insomnia, IBS, and CF, indicating that selection bias may not be a substantial problem.[11,13,15,16] A survey including 4622 people aged 30 to 75 years from Norway reported that 388 (8.4%) had IBS according to Rome II criteria.[16] The difference in prevalence between the control group in our study and this reference population correlates with findings in studies comparing prevalence based on Rome II and Rome III criteria.[17–19] Another study using the FQ in a survey of the general population in Norway reported a prevalence of 10.5% for CF in the age group 30 to 49 years.[13] The control group showed similar levels of sleepiness as reported in the general population, where it has been reported 6.95 hours as mean hours of sleep.[11] The exposed group had a high response rate (65.3%). Still, selection bias cannot be ruled out in this group as exposed individuals not experiencing trouble sleeping or daytime sleepiness might have been less interested in responding. To be included in the questions on daytime sleepiness, all 8 ESS questions had to be answered. Another limitation with the sleep questions is that we have no information about daytime sleepiness, insomnia, or sleep need before the exposure to *Giardia* infection.

Table 7
Results from multiple linear regression analyses[a] of self-reported sleep need in the presence of IBS, CF, and *Giardia* exposure for 817 exposed and 1128 controls in the *Giardia* epidemic in Bergen, Norway, 2004.

	Self-reported sleep need		
	b	95% CI	*P*
Intercept	6.55	5.56-7.53	<.001
Giardia-exposed	0.12	0.01-0.24	.040
IBS	0.27	0.14-0.40	<.001
CF	0.78	0.65-0.92	<.001
	$R^2 = 0.227$; adjusted $R^2 = 0.219$		

Adjusted for age, gender, marital status, education, employment status, and student status in 2004.
Abbreviations: *b*, estimated regression coefficient; CI, confidence interval; IBS, irritable bowel syndrome; CF, chronic fatigue; R^2 = determination coefficient.
[a] No significant interactions were found.

Insomnia and self-reported sleep need were examined in our study by single questions previously used in a large epidemiologic Norwegian study (HUSK) among 40- to 45-year-old individuals.[15] This study showed that average sleep need was 7 hours, 16 minutes in men and 7 hours, 45 minutes in women. Insomnia was reported in 10% of men and 12.2% of women. In our study, we found the mean sleep need in the *Giardia*-exposed group to be 8 hours and 7 hours 30 minutes in the control group, including both women and men of all ages. Insomnia was reported in 15.4% of the *Giardia*-exposed and 8.8% of the controls. Our control group showed results similar to the previous Norwegian population–based study. The *Giardia*-exposed had a self-reported sleep need clearly higher than that reported in the general Norwegian population. This increased sleep need was not solely explained by concomitant CF and IBS, as shown by the multiple linear regression analysis.

In our study, both *Giardia*-exposed and controls with CF had more daytime sleepiness than did participants without CF. A previous study looked at patients with CFS (n = 16), patients with excessive daytime sleepiness as seen in sleep apnea-hypopnea syndrome (n = 13), and healthy controls (n = 12).[9] Subjective sleepiness was measured by ESS. No significant difference in ESS score was seen between the 2 patient groups, but the patients with CFS reported a higher level of fatigue as compared with the sleep apnea-hypopnea syndrome group. Compared with the healthy controls, the CFS patients were both more fatigued and sleepier. Our study showed a similar pattern where the participants with CF also scored higher on daytime sleepiness.

We have investigated the association between *Giardia* exposure and daytime sleepiness, insomnia, and self-reported sleep need, respectively. There is limited research on the long time effects of infections on sleep, but in a case-control study, Macsween et al[2] looked at how sleep and daily activity were affected after infection with Epstein-Barr virus. The group that had gone through infection had significantly higher sleep need than did the control group from the time of diagnosis and up to 150 days after. This correlates with our findings that sleep need increases after *Giardia* infection.

We also investigated the relationship with concomitant IBS and/or CF. The conclusion is that being exposed to *Giardia* was independently associated with excessive daytime sleepiness and experiencing larger sleep need, but not with insomnia. IBS and CF are prevalent disorders in the *Giardia* group. Both disorders and, particularly CF were strongly associated with daytime sleepiness, insomnia, and increased sleep need. This is in line with previous studies on fatigue and sleep disorders in other patients. In patients with multiple sclerosis, fatigue was associated with both excessive daytime sleepiness and insomnia.[20] A review of the research on cancer-related fatigue and sleep disorders concluded that cancer-related fatigue is strongly associated with both impaired sleep quality and excessive daytime sleepiness.[21]

Our study shows the need to consider several aspects of sleep disturbances in relation to both infections and other post-infectious complications.

Disclosure

The authors have no conflicts of interest.

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PAPER 3

Observational Studies

Gunnhild S. Hunskar*, Guri Rortveit, Sverre Litleskare, Geir Egil Eide, Kurt Hanevik, Nina Langeland and Knut-Arne Wensaas

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

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Abstract

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

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

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

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

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

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Introduction

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

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

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

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

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

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

Methods

Study design

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

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

Variables

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

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

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

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

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

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

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

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

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

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

Statistical analyses

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

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

Results

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

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

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

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

Discussion

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

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

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

Prevalence of fibromyalgia

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

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

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

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

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

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

Overlap of fibromyalgia, IBS and CF/CFS

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

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

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

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

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

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

Strengths and limitations

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

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

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

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

Conclusions

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

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Questionnaires

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?
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☐ 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.

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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?
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☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

23. Har du vansker med å konsentrere deg?
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24. Forsnakker du deg i samtaler?
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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!

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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

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10. Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
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25. Er det vanskeligere å finne det rette ordet?
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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!

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
postadresse Postboks 7810, N-5020 Bergen
telefon +47 55 58 61 41 **telefaks** +47 55 58 61 30
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organisasjonsnummer 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

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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

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

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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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