HHS Public Access

Author manuscript

Fatigue. Author manuscript; available in PMC 2019 January 19.

Published in final edited form as:

Fatigue. 2018 ; 6(2): 106–121. doi:10.1080/21641846.2018.1426086.

The International Collaborative on Fatigue Following Infection (COFFI)

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Abstract

Background: The purpose of the Collaborative on Fatigue Following Infection (COFFI) is for investigators of post-infection fatigue (PIF) and other syndromes to collaborate on these enigmatic and poorly understood conditions by studying relatively homogeneous populations with known infectious triggers. Utilizing COFFI, pooled data and stored biosamples will support both

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epidemiological and laboratory research to better understand the etiology and risk factors for development and progression of PIF.

Methods: COFFI consists of prospective cohorts from the UK, Netherlands, Norway, USA, New Zealand and Australia, with some cohorts closed and some open to recruitment. The 9 cohorts closed to recruitment total over 3,000 participants, including nearly 1000 with infectious mononucleosis (IM), > 500 with Q fever, > 800 with giardiasis, > 600 with campylobacter gastroenteritis (CG), 190 with Legionnaires disease and 60 with Ross River virus. Follow-ups have been at least 6 months and up to 10 years. All studies use the Fukuda criteria for defining chronic fatigue syndrome (CFS).

Results: Preliminary analyses indicated that risk factors for non-recovery from PIF included lower physical fitness, female gender, severity of the acute sickness response, and autonomic dysfunction.

Conclusions: COFFI (https://internationalcoffi.wordpress.com/) is an international collaboration which should be able to answer questions based on pooled data that are not answerable in the individual cohorts. Possible questions may include the following: Do different infectious triggers different PIF syndromes (e.g., CFS vs. irritable bowel syndrome)?; What are longitudinal predictors of PIF and its severity?

Why was the Collaborative set up?

The purpose of the Collaborative on Fatigue Following Infection (COFFI) is for investigators of post-infection fatigue (PIF) and other syndromes to collaborate on these enigmatic and poorly understood conditions by studying relatively homogeneous populations with known infectious triggers. COFFI was established following a meeting at the Royal Society of Medicine (June 2015) in London, attended by principal investigators studying post-infection cohorts in the UK, Netherlands, Norway, USA, New Zealand and Australia.

Fatiguing Illness Definitions

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis or systemic exertion intolerance disorder (SEID) is a prevalent, but enigmatic and poorly understood condition.[1] CFS is usually defined by the Fukuda (Centers for Disease Control [CDC]) diagnostic criteria. [2] Both the Fukuda and the (broader) Oxford criteria require ≥ 6 months of severe/disabling fatigue that affects physical and mental functioning, and excludes established medical and psychiatric diagnoses that may explain presenting fatigue.[3]

Similarly, the Canadian consensus criteria require ≥ 6 months of fatigue, but also require several additional symptoms including: post-exertional malaise, sleep dysfunction, pain, two or more neurological manifestations, and at least one of the following: autonomic, neuroendocrine or immunologic symptoms,[3a] Recently proposed criteria for SEID specify fatigue for 6 months that impairs activity and includes post-exertional malaise and unrefreshing sleep, plus cognitive difficulties or orthostatic intolerance, but have no exclusionary criteria.[4] Chronic fatigue (CF) alone is defined as symptomatic fatigue lasting 6 months or more without additional symptom requirements.

Certain infective illnesses such as infectious mononucleosis (IM) are the only evidence-based triggers of CFS.[5–7] Motivation for a collaborative of investigators of post-infection cohorts is threefold. First, certain infections including IM caused by Epstein-Barr virus (EBV) have been reliably implicated in triggering CFS and therefore provide a known point of time for illness onset. Second, following a cohort after a known infectious trigger allows for greater homogeneity of the patient population being studied, improving reproducibility of findings.[8,9] Third, a research collaborative offers greatly increased power to support both epidemiological and laboratory research, to better understand the etiology and risk factors for development and progression of PIF.

Despite the fact that the fatigue being studied is post-infection, no evidence exists for persistence of the triggering microbe (e.g., EBV) in patients with CFS.[10,11] Instead, the underlying hypothesis of the collaborative is that prolonged fatigue after infection is a consequence of biologic, behavioral and/or environmental effects, in which susceptible individuals develop alterations in neurobehavioural, cardiovascular and/or immunological systems. In addition, the Collaborative seeks to determine whether different triggers (e.g., IM vs giardiasis) lead to different post- infectious consequences (e.g., CFS vs. irritable bowel syndrome [IBS][12]). The overall aim of the Collaborative is to characterize and identify risk factors for post-infection fatigue. The specific research questions that COFFI aims to answer are listed in Table 1.

What Cohorts are in the Collaborative?

At its inception, COFFI comprised the cohorts listed in Tables 2 and 3, of which some are closed (Table 2) and some still open (Table 3) to recruitment. All studies were approved by the appropriate Institutional Review Boards, with consents being obtained as required. The nine cohorts closed to recruitment included > 3,000 participants whose illnesses began with an infectious event as follows: nearly 1000 with IM/glandular fever (4 cohorts), > 500 with Q fever (2 cohorts), > 800 with giardiasis (1 cohort), > 600 with campylobacter gastroenteritis (CG; 1 cohort), 190 with Legionnaires disease (1 cohort) and 60 with Ross River virus (RRV; 1 cohort). Some of the studies had comparison groups of healthy controls or patients with an upper respiratory tract infection. All studies were prospective. For more details, see Table 2.

Regarding the open studies (Table 3), one is following a well population who may then develop IM, in an attempt to isolate pre-illness risk factors, and two are following patients with various infective triggers.

Generally follow-up is at least 6 months, with many studies following participants out to 12 and 24 months, and some for up to 10 years (Tables 2 and 3).

What has been measured?

The two main outcomes of interest to COFFI are the development of CF and CFS. The measures of fatigue, the diagnostic criteria, and other questionnaire-derived data and/or biosamples are summarized in Tables 2 and 3. Some studies followed cohorts with gastrointestinal tract infectious triggers, and measured development of IBS and/or functional

dyspepsia as well as CFS. Biosamples have also been collected and are banked by most of the studies. A range of assay data are available, or will be available (Tables 2 and 3).

What has been found?

Epidemiology

The prevalence of CFS following IM varied from 8 – 22 % at 6 months (although most studies showed a 9 – 13% prevalence) and 7–9% at 12 months (Table 4). Following other infectious diseases within the Collaborative, the rates of post-infectious fatigue and other sequelae were higher, but so were the rates of fatigue and other symptoms in the control subjects. This may reflect the differing propensity of different pathogens to trigger CFS; however, less rigid definitions of CF, CFS or IBS will also result in higher rates of diagnoses of CF, CFS and/or IBS in both controls and study subjects.

A previous meta-analysis indicated a prevalence of CFS of 0.76% (95% CI 0.23% to 1.29%).[13] Milder infections such as upper respiratory tract infections did not to lead to CF or CFS at the same rate as more serious infections such as IM.[5,14,15]

Bergen Giardiasis Cohort

The Bergen giardiasis cohort was initiated following an outbreak of giardiasis in 2004: >48,000 people were exposed and 2,500 became ill, including 1,252 verified giardiasis cases.[16] Follow-up for fatigue has been as long as 10 years. At 3 years' post-infection, 1,252 cases and 3,598 matched controls were contacted, with response rates of 65% (n=817) and 31% (n=1128), respectively.[14] Prevalence of CF was 46% among cases and 12% among controls; for severe CF (CF plus an elevated fatigue score), prevalence was 15% among cases and 2% among controls; and for consistent CF (CF present at least 85% of the time), prevalence was 18% among cases and 5% among controls. Relative risks for CF was 4.0 (3.5 to 4.5), for severe CF, 7.4 (4.9 to 10.9), and for consistent CF, 3.6 (2.6 to 4.7).

Of 366 fatigued participants at 3 years follow-up, 253 were invited to a 5-year fatigue assessment. Of the 53 who responded, 22 met criteria for CFS, 7 had idiopathic CF, 13 had CF due to other causes, and 11 had recovered.[17] Prevalence of IBS 3 years after giardiasis was 46% in cases and 14% in controls; for severe IBS (defined as limiting or restricting daily activity at least "often"), prevalence was 14% in cases and 3% in controls, and for frequent IBS (defined as pain or discomfort at least 1 day per week), the prevalence was 22% in cases and 4% in controls. The calculated relative risks for developing IBS, severe IBS and frequent IBS following giardiasis were, respectively, 3.4 (2.9 to 3.8), 5.1 (3.6 to 7.2) and 6.2 (4.5 to 8.3). At 6 years post-infection, the relative risk for IBS was unchanged at 3.4 (2.9 – 3.9), whereas the relative risk for CF was lower at 2.9 (2.3 – 3.4). The incidence of CF or IBS following giardiasis seemed to be about the same after 3 years, but IBS persisted more often than CF after 6 years.[18]

Auckland CG and IM cohort

The Auckland (New Zealand) Campylobacter gastroenteritis (CG) and IM cohort study followed patients with CG (as a potential trigger for IBS) and IM (as a potential trigger for

CFS).[12] At 6 months, 11% of CG patients and 8% of IM patients had IBS; 5% of CG patients and 8% of IM patients had CFS; 7/118 (6%) of identified cases met self-reported criteria for both CFS and IBS. After controlling for age and gender, there was a trend for IM to be associated with CFS, compared with CG (OR 1.48 [0.62 to 3.55]). The odds of IBS were 2-fold higher post-CG compared with post-IM (OR 2.22 [1.11 to 6.62]).

The role of biopsychosocial factors in post-infection fatigue was also explored in the Auckland CG and IM study, based on a cognitive behavioural explanatory model of predisposing, precipitating and perpetuating factors.[12] In this model, fatigue precipitated by infection and/or stress is perpetuated by cognitive (e.g. “I must not let this get the better of me”), behavioural (all-or-nothing behaviour), mood (anxiety/depression) and biological (e.g., poor sleep, deconditioning) responses. Specific research questions asked were: 1) Does the nature of the moderate to severe infection determine the specific syndrome?, and 2) Are the predisposing and perpetuating psychological factors common across the syndromes?[20,21] The study collected self-reported measures of anxiety, depression, perfectionism, perceived stress, behavioural response to illness, activity, rest, all-or-nothing behaviour, and illness perception. Several self-reported factors emerged as predictors of IBS and CFS which were consistent with a cognitive behavioural model for both syndromes, namely: somatisation, anxiety, negative illness/symptom beliefs, and all-or-nothing behaviour.[20,21] Depression was a risk factor for CFS but not IBS.

Barts IM Cohort

Predictors of post-infectious fatigue in the Barts IM cohort (see Table 2) at 6 months included: a positive monospot test at onset and lower physical fitness at one month follow-up.[19] Cervical lymphadenopathy and duration of initial bed rest predicted a fatigue syndrome at 2 months but not 6 months. Neither past mood disorders nor life events predicted a fatigue syndrome at 6 months, in the absence of a comorbid mood disorder.

Prospective Study of IM (Seattle)

The ‘Prospective Study of the Natural History of IM Caused by EBV’ study (Seattle) reported three factors associated with failure to recover from IM: female gender (OR 3.3 [1.0 to 12]); a greater number of traumatic life events more than 6 months before the disease began (OR 1.7 [1.1 to 2.5], per each additional life event); and greater family support (OR 1.9 [1.1 to 4.2]).[6] No objective measures distinguished patients who did recover from those who did not. Baseline psychiatric disorders and psychological distress were not associated with non-recovery. Older age, higher basal temperature, and greater impairments in physical functioning at baseline (shortly after illness onset) were associated with self-reported non-recovery at 2 months, but not at 6 months. This disparity may indicate that the subacute, 2-month predictors were determined primarily by biological factors, whereas the chronic, 6-month predictors represented a more complex mix of psychological and social factors.

Dubbo Infection Outcomes Study

The Dubbo Infection Outcomes Study showed that the type of infectious trigger was less important than the severity of the acute infectious illness. Furthermore, no differences were found in immune responses or leucocyte transcriptome profiles beyond the acute phase

between post-infectious fatigue cases and matched recovered controls.[22–26] These investigators also found substantial individual variation in the overall severity of the acute sickness response and in specific symptom manifestations among people infected with the same pathogen. These endophenotypes, or individual symptom profiles, were stable over time within subjects with ongoing CFS. In the acute phase, serum levels of the pro-inflammatory cytokines, interleukins IL-1 and IL-6, were correlated with symptoms, functional polymorphisms in cytokine genes (interferon-γ, IL-6 and IL-10), and with the severity of the acute sickness response.[25,27] However, longitudinal analysis of cytokine production found no differences between levels of these cytokines in patients with/without persistent symptoms up to 12 months post-infection.[24] This is consistent with a recent systematic review which found no differences in levels of circulating cytokines, with the possible exception of higher levels of transforming growth factor-β, among CFS cases compared with controls.[28]

Dutch Q-fever Cohorts

The Dutch Q-fever cohort studies were initiated after approximately 4,000 patients with Q-fever were identified in the Netherlands between 2007 and 2010.[29] These studies included cohorts comprising approximately 336 Q-fever patients who experienced onset of illness between 2010 and 2011. Patients with Q-fever were compared with: a) patients (at 12 months) with Legionnaires' disease (N=190)[30,31]; and b) healthy controls (at 24 months; N=130)[32]. Q-fever cases improved over 24 months, but many still reported poor health. Several risk factors were identified: female gender, younger adults, having pre-existing health problems, consuming no alcohol, using medication, being hospitalised in the previous 3 months, and receiving additional treatment for Q-fever.

Ongoing and Recently Completed Studies

CFS Following IM in College Students (Chicago)

The three ongoing cohort studies within COFFI are continuing to enrol participants and/or collect data. The first is an National Institutes of Health (NIH)-funded study in Chicago, which builds upon the lead investigators' findings from an earlier cohort study which followed 301 adolescents with monospot-positive IM in the greater Chicago area.[7] In the earlier study, 39 (13%) participants met criteria for CFS at 6 months, 22 (7%) met criteria at 12 months, and 13 (4%) met criteria at 24 months. Exercise tolerance testing at 6 months found no difference in peak work capacity between CFS and non-CFS participants, but adolescents with CFS had a lower degree of fitness and exercised less efficiently than recovered controls.[34]

Morning cortisol was reduced in 3/9 cases *versus* 1/9 controls[35], and some differences were found in network cytokine expression profiles as well[36]. This is somewhat different from the findings in the Dubbo study,[24] although not all cytokines studied were the same and the participants in the Chicago study were younger. Finally, cases and recovered controls completed an Autonomic Symptom Checklist at baseline (~2 months post-IM) and at 6, 12 and 24 months post-IM, with substantial differences evident at each time point.[37] Several biologically plausible hypotheses can be addressed: Is there an autonomic predisposition to

non-recovery from IM, or does (severe) IM lead to CFS? These hypotheses can only be addressed by prospective studies beginning when subjects are well (Table 3). If a single study does not have the power to resolve the issue, pooling data from > 1 study very well might.

Chronic Fatigue Following Acute EBV Infections in Adolescents (Norway)

The CEBA study[39] (see Table 2) recruited 200 adolescents (age 12–19 years) with serologically-confirmed EBV+ IM and 70 healthy controls. This ongoing study has a 6-month follow-up period, followed by a randomised controlled intervention for 60 subjects with EBV infections and persistent fatigue, to test cognitive behavioural therapy (CBT) and music therapy against routine care, with follow-up to 15 months. Perpetuating factors to be studied include: cognitive, endocrinologic, autonomic and immune function. Participants will also undergo functional MRI and semi-structured interviews. The first part of the study concluded in June 2017; data are currently being analysed (see Table 2).

Sydney Infectious Outcomes Study

The Sydney Infectious Outcomes Study (SIOS; see Table 3) builds upon the Dubbo study. SIOS has been recruiting subjects with any acute febrile (presumed viral) illness (≥38°C) with systemic features (e.g. myalgia), for enrolment within 48 hours of onset and characterisation of the acute sickness response. An initial finding in SIOS has been a reduction in heart rate variability (HRV; indicative of autonomic disturbance) among subjects with post-infectious fatigue, and low HRV was strongly associated with unrefreshed sleep[40]. By contrast, subjects with a greater increase in HRV also had a shorter duration of illness, and this increase in HRV also had an inverse correlation with the serum inflammatory marker C-reactive protein.

In combination with the findings from the Chicago IM study, these SIOS data support a potential role for the autonomic nervous system in the development of CFS.[37,40] Studies in SIOS are focusing also on disturbances in circadian rhythm and biological correlates of fatigue when exacerbated by physical exercise or cognitive challenge.[41]

Bergen Giardiasis Study

The Bergen giardiasis study has completed follow-up of participants at 10 years' post-infection: 1,176 cases and 2,330 matched controls have been contacted, with response rates of 50% (n=590) and 30% (n=696), respectively. Cases and controls were assessed for IBS, CF and fibromyalgia, and DNA samples are being analysed by the Genes in Irritable Bowel Syndrome Research Network Europe (GENIEUR) study.

Qure Study

Another recently completed study is the Qure study (Table 2), a 3-arm randomized controlled trial (N=154) of treatment of Q-fever fatigue syndrome with CBT *vs* doxycycline *vs* placebo at 6 months.[42] These recently published results showed that doxycycline treatment had no significant effect on fatigue 6 months after Q fever diagnosis compared to placebo (3.0 percentage points lower with placebo vs doxycycline), unlike CBT which

reduced fatigue 6.2 percentage points more than placebo (p=0.03). Finally there is the FAME study (see Table 3) from the University of Southampton.[43]

What are the main strengths and weaknesses of COFFI?

The strongest elements of COFFI are the inclusion of new (and future) cohort studies. The older cohorts are limited to provision of biosamples and data for meta-analyses of prevalence and risk factors. Additional infectious disease outbreaks are potential avenues for further research and collaboration within the COFFI network. The main limitation is the relatively small number of cases of post-infection CFS, but again, pooling of data will increase the power of future meta-analyses. Also, in the past, different cohorts did not always use the same measures. As the COFFI Network progresses, we hope to be able to standardize the methods used across studies.

Uniform classification of CFS across studies

All the COFFI studies which had CFS as an outcome use the Oxford or Fukuda diagnostic criteria for CFS.[2,3] Other studies that have used CF [30,32,44] usually also report on individuals meeting the Fukuda criteria for CFS, again allowing for pooling of data.

Standardization of other patient-reported and clinical measurements may be problematic, given the wide range of instruments used (Tables 2 and 3). The current NIH effort to standardize Common Data Elements with which to study CFS will be crucial to facilitate future data pooling. Similarly, standardization of measurement of key predictive factors (e.g., the severity of the acute infection) and indicators of social adversity across studies will be needed if data are to be successfully pooled.

Homogeneity of the patient populations studied

COFFI circumvents a key issue of patient heterogeneity in studies of the prevalence of CFS [44,45] in that all CFS cases in COFFI follow a documented infectious event. Pooled analyses may still need to consider CFS endophenotypes such as those which can be defined by different symptom profiles or those that result from different infectious triggers (e.g., IM or Q fever vs Campylobacter or Giardia infection).[46, 47]

Can I get hold of the data? Where can I find out more?

Readers who wish to find out more should visit the COFFI website at www.internationalcoffi.wordpress.com or contact the corresponding author. COFFI is modelled on the successful InC^3 International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts,[48] that encourages the participation of interested investigators. As COFFI evolves, it is anticipated that new cohorts will be invited to participate, to expand the geographic and population representation in the collaboration.

COFFI will be governed by an Executive Committee, comprising the COFFI lead investigator (Chair), project coordinator, data leader and specimen leader. A COFFI Steering Committee will comprise the above persons, plus the Principal Investigator(s) from each of the participating studies. Standard Operating Procedures will be developed to define COFFI

policy on data and sample sharing, authorship, admission of new cohorts, and consideration of research proposals, e.g. requests for patient specimens. In addition, COFFI will invite the participation of subject matter experts in statistics, virology, genetics, etc. where such expertise is not found among COFFI members.

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Table 1:

COFFI Research Questions

Q1	Do different infections trigger different post-infection syndromes?
Q2	What are the predictors of long-term symptoms following infection?
Q3	Are there qualitative differences in fatigue following infection and, if so, what factors predict any such differences?
Q4	Are there predisposing risk factors for post-infection fatigue before or during the febrile phase?
Q5	Are there early or late perpetuating risk factors for post-infection fatigue?
Q6	How do the risk factors and/or perpetuating factors interact and change over time?
Q7	What are therapeutic options for post-infection fatigue?

Table 2:

Closed COFFI cohorts

Cohort name, Country	Major Reference(s)	Participants	Follow-up	CFS Definition(s) Used	Questionnaires/ Data Collected	Samples Collected	Assay Data	Other Investigations
Barts Infectious Mononucleosis (IM) cohort, UK	White 1998[5]	469 primary care patients approached, 250 recruited, 245 eligible: 108 IM confirmed Epstein-Barr Virus (EBV), 83 non-EBV IM-like, 54 URTI controls	1, 2 & 6 months, patient records to 2.5 years	Empirical fatigue syndrome, Centers for Disease Control (CDC)/ Fukuda, Oxford	20 infectious symptoms, Hospital Anxiety and Depression Scale (HADS), Eysenck Personality Questionnaire (EPQ), days spent in bed, premorbid GP attendance, Research Diagnostic criteria for psychiatric illness), Life Events and Difficulties Schedule, Paced Auditory Serial Addition Test, Present State Exam, Clinical Interview Schedule, Hamilton Depression Rating Scale, Schedule for Affective Disorders and Schizophrenia	Serum, T cells, mouth wash (no longer available)	EBV, Cytomegalovirus (CMV), Human Herpesvirus 6. Hepatitis A and C, toxoplasmosis, adenovirus, influenza A and B, parainfluenza, Respiratory Syncytial Virus, *Coxiella burnetti*, *Mycoplasma pneumonia*, *Chlamydia psittaci* and anti-strepotolysin O antibodies, liver chemistries, B cell regression assay.	Exercise work capacity, cardiovascular response to exercise
Prospective Study of the Natural History of IM Caused by EBV (Seattle,USA)	Buchwald 2000[6]	Puget Sound area health maintenance organisation primary care facilities, 150 IM patients recruited; 146 at 1 month, 144 at 2 months, 142 at 6 months, 50 at 48 months	1, 2, 6 & 48 months	Not necessarily CFS	Symptom Checklist-90, Short Form (SF)-36, NIH Mental Health Diagnostic Interview Schedule, List of Threatening Experiences, Perceived Social Support Inventory	Serum	Complete blood count with a differential leukocyte count, serum AST, ALT, bilirubin level, and EBV titres.	
Dubbo Infection Outcomes Study (DIOS), Austrralia	Hickie 2006,[38] Cameron 2006,[22] 2007,[23] 2010,[26] Vollmer-Conna 2007,[24] Kadota 2010[40]	Laboratory notifications for 855 potential participants from 94 primary care practitioners, 430 contacted, 253 recruited: 68 confirmed EBV, 60 confirmed Ross River Virus, 43 confirmed Q fever, 82 unconfirmed	2 & 6 weeks; 3, 6 & 12 months, and then 6 monthly until recovery (for cases) for at least 5 years	CDC/ Fukuda/ post-infectious fatigue syndrome/ acute sickness response	Structured Clinical Interview for Neurasthenia; Prolonged fatigue state (score ≥3) on SOMA somatic symptoms subscale of 34-item Somatic, Psychological Health Report, Physical symptoms Checklist, McGill Pain Questionnaire, Alcohol Use Disorders Identification Test, SF-36, Sleep Assessment Questionnaire, Brief Disability Questionnaire (BDQ), Health Care Utilization, EPQ, Locus of Control of Behaviour Scale, Illness Behaviour Questionnaire, Illness Impact	DNA, RNA, plasma, Peripheral blood mono-nuclear cells		Serum and stimulated cytokine levels, transcriptomics, genetic polymorphisms (e.g., cytokines).
Prospective Study of CFS Following IM (Chicago, USA)	Katz 2009,[7] 2010,[34] 2011,[37] 2013[35] Broderick 2012[36]	N=301 adolescents (12–18) with heterophile-positive IM	6, 12 and 24 months following illness	CDC/Fukuda	Autonomic Symptom Checklist, Orthostatic Tolerance Testing, Fatigue Severity Scale, Modifiable Activity Questionnaire, CFS Screening Questionnaire, Occupational Health Assessment, Child Health Questionnaire	Serum, Plasma, Saliva, Urine		Exercise testing, Orthostatic Tolerance Testing, CBC, metabolic, endocrine testing, urinalysis, erythrocyte sedimentation rate, cytokine analysis, salivary cortisol, Natural Killer cell number and function
CEBA (Chronic fatigue following acute EBV infection in Adolescents), Norway	Clinicaltrials.gov	Laboratory identification of IM cases from AHUS University Hospital: 200 adolescents with EBV; 70 healthy controls	6, 9 & 21 months	Canadian, CDC/ Fukuda, Institute of Medicine	Chalder Fatigue Questionnaire score ≥4 (range 0–11), Autonomic Symptom Profile, Peds-QL, Functional Disability Inventory, Brief Pain Inventory, Life Event Checklist, HADS, Child-Adolescent Perfectionism Scale, Toronto Alexithymia Scale-20 item, Brief Illness Perception Questionnaire, Karolinska Sleep Questionnaire, The Penn State Worry Questionnaire, Wechsler Intelligence Scale for Children, Delis-Kaplan Executive Function System, Hopkins Verbal Learning Test-Revised, Wechsler Abbreviated Scale of intelligence	Blood (serum, plasma, peripheral blood mono-nuclear cells), urine (morning spot), hair	EBV-DNA by real-time PCR; anti-EBV EBNA IgG and Viral Capsid Antigen IgG and IgM; antibodies against CMV and *Borrelia burgdorferi*; cytokines; plasma catechol-amines; candidate gene single nucleotide polymorphisms; number and cytotoxic function of natural killer cells; cortisol from urine and hair	Accelerometers for monitoring of daily physical activity during seven consecutive days; algometer for assessing pain threshold; cardiovascular assessment ; cognitive assessment.
Auckland IM & Campylobacter gastroenteritis cohorts, NZ	Spence 2007,[21] Moss-Morris and Spence 2006;[12] Moss-Morris *et al* 2011[20]	Laboratory identification of 2547 CG cases, ~1500 questionnaires sent, 758 returned, 620 recruited: CG (n=592); after 3	3 and 6 months	British (Sharpe), CDC/ Fukuda	HADS, Illness Perceptions Questionnaire - Revised, Perceived Stress Scale, Behavioural Responses to Illness Questionnaire, The negative subscale of the Positive & Negative Perfectionism Scale	None	None	

Cohort name, Country	Major Reference(s)	Participants	Follow-up	CFS Definition(s) Used	Questionnaires/ Data Collected	Samples Collected	Assay Data	Other Investigations
		months N = 581, after 6 months N = 547						
Dutch Q fever (and LRTI & Legionnaires' disease) studies: **- Cohort 2010–11** **- Legionnaires' disease**	**Cohort 2010–11:** Van Loenhout, J of Inf 2015[31] **Legionnaires' disease:** Van Loenhout, J of Inf 2014[30]	**Cohort 2010–11:** Eligible: 376 Participated: 336 Drop-outs: 58. **Legionnaires' disease:** Eligible: 243 Included: 190	**Cohort 2010–11:** 3, 6, 9, 12, 18, and 24 months **Legionnaires' disease:** 12 months after onset illness	No CFS diagnosis used. (Laboratory confirmed Q fever; applies for all Q fever patients in the cohorts)	**Cohort 2010–11:** Short Form 36 (SF-36) and Nijmegen Clinical Screening Instrument (NCSI) **Legionnaires' disease:** SF-36 and NCSI questionnaire			
Qure Study, NL	Keijmel 2017[42]	180 Q fever patients randomised to 6 months' cognitive behavioural therapy(CBT), 60 doxycycline or 60 placebo; follow-up to 12 months post-treatment intention to treat analysis, N = 154, 52 doxycycline, 52 placebo, 50 CBT.	12 months	Q fever Fatigue Syndrome – diagnostic criteria similar to CDC/Fukuda but requiring laboratory-proven acute Q fever in the context of an acute illness with fever	Sickness Impact Profile Symptom Checklist 90, Self Observation List, Checklist Individual Strength	No study-specific samples collected. Routinely-collected sera may have been stored from time of initial diagnosis.	*C burnetti* serology, liver enzymes, doxycycline levels	Actometer
Bergen Giardiasis cohort, Norway	Wensaas 2012,[14] Morch 2013,[17] Hanevik 2014[18]	Laboratory notified giardiasis (2004 outbreak, N=1252); age/ gender-matched controls: n=817 at 3 years, 748 at 6 years, 590 at 10 years At 5 years, 53 of 253 assessed for CFS	3, 5, 6 and 10 years	CDC/ Fukuda	Chalder Fatigue Questionnaire score ≥4 (range 0–11); Rome III diagnostic questionnaire for irritable bowel syndrome and functional dyspepsia.	Stool, Serum and PBMC in subgroup of patients	*Giardia lamblia* cysts detected by direct microscopy or by a faecal antigen test (ImmunoCard STAT! Cryptosporidium/ Giardia rapid assay; Meridian Bioscience, Inc)	Sleepiness (3, & 6 years), Asthma and allergy (3, & 6 years), Overactive bladder (6 years), Fibromyalgia (10 years)

Table 3:

Open COFFI cohorts

Cohort name, Country	Principal Investigator(s)	Participants	Follow-up	CFS Definition(s) Used	Questionnaires/ Data Collected	Samples Collected	Assay Data	Other Investigations
Sydney Infection Outcomes Study (SIOS), Australia	Ute Vollmer-Conna, Andrew Lloyd	Attendees at University Medical Health Service and Emergency Department (Prince of Wales Hospital) with acute, febrile viral infection	2, 12 & 24 weeks	CDC/ Fukuda	Prolonged fatigue state (score ≥3) on somatic symptoms subscale of 34-item Somatic and Psychological Health Report; International Neuropsychiatric Interview, Structured Clinical Interview for Neurasthenia, Symptom Checklist (current physical symptoms), Kessler Psychological Distress Scale, Pittsburgh Sleep Quality Index, McGill Pain Questionnaire, SF-36, Perceived Stress Questionnaire, Duke Social Support Index, EPQ, Somatosensory Amplification Scale, Childhood Trauma Questionnaire – Short Form, AUDIT alcohol consumption questions, Health Care Utilization	At each assessment visit, ~ 90ml of venous blood are collected: 1 red top; 1 white top (6 ml with 120μl of EDTA/ glutathione added), 8 yellow top tubes (72ml in ACD)	Stored RNA and genomic DNA (host genetic and gene expression analyses), stored PBMCs (for cytokine production assays), stored serum/ plasma (for bioplex assays, CRP, neopterin, neuropeptide Y, catecholamines, vitamin D).	Circadian rhythm, autonomic function testing
CFS following IM in college students (Chicago, USA)	Ben Katz, Leonard Jason	Attendees at Northwestern University Health Service: Stage 1 - healthy college students (N=3661 as of 5/26/16); Stage 2 - identify IM cases (N=155 as of 5/26/17; Stage 3 (6 months following IM) - compare those who develop CFS (n=21 @ 6 months) with matched controls (n=23 as of 5/26/17)	6 & 12 months	CDC/ Fukuda; IOM; Canadian criteria	Compass 31 (an autonomic symptom checklist), Perceived stress scale, Modified activity questionnaire, Coping orientation to problems experienced scale, Beck Depression Inventory, Beck Anxiety Inventory, Fatigue Scale	Plasma, serum, viable cells	Complete blood count, comprehensive metabolic panel, CRP, urinalysis, thyroid function, HIV antibody test, urine toxicology, Beta HCG.	
FAME (acute Fatigue Assessment and Management in Everyday practice), UK	Paul Little	Primary care attendees (10 practices) over 4 months: 150–200 acute fatigue patients comprising groups with sore throat, other infection, and no infection. (baseline and 6 months)	6 months			Blood and urine	Samples for storage only currently.	Website to support self-management

Fatigue. Author manuscript; available in PMC 2019 January 19.

Table 4.

COFFI Closed Cohort post-infection outcomes

	CASES	CASES	CONTROLS	CONTROLS
Cohort	**CF/S**	**IBS**	**CF/S**	**IBS**
Barts Infectious Mononucleosis (IM) cohort, UK (White, 1998[5])	9–22% CFS @ 6 mos. following IM, depending upon CFS definition used		0–6% CFS @ 6 mos. following URI depending upon CFS definition used	
Prospective Study of the Natural History of IM Caused by EBV (Seattle, USA) Buchwald, 2000[6]	12% of IM failed to recover @ 6 mos.			
Dubbo Infection Outcomes Study (DIOS), Austrralia. (Hickie 2006[38])	12% CFS @ 6 mos., 9% @ 12 mos. following IM, Q fever or RRV			
Prospective Study of CFS following IM (Chicago, USA) (Katz 2009[7])	13% CFS @ 6 mos., 7% @ 12 mos., 4% @ 24 mos. following IM			
CEBA (Chronic fatigue following acute EBV infection in Adolescents), Norway; Clinicaltrials.gov	June 2017: Data being analyzed			
Auckland IM & Campylobacter gastroenteritis (CG) cohorts, NZ (Spence 2007[21])	8% CFS @ 6 mos. following IM 5% CFS @ 6 mos. following CG	8% IBS @ 6 mos. following IM 11% IBS @ 6 mos. following CG		
Dutch Q fever (and Legionnaires' disease) studies: Cohort 2010–11; Legionnaires' disease (Van Loenhout 2014,[30] 2015[31])	60% severe fatigue @ 12 mos. and 37% @ 24 mos. following Q fever 50% severe fatigue @ 12 mos. following Legionnaire's disease			
Qure Study, NL (Keijmel 2017[42])	42% CFS @ 5 years following Q fever 8–19% @ 10 years following Q fever	26% CFS @ 5 years following Q fever 0–4 % @ 10 years following Q fever		
Bergen Giardiasis cohort, Norway (Wensaas 2012,[14] Hanevik 2014[18])	15–46% CF @ 3 years (depending on severity) and 9–31% @ 6 years following giardiasis	13–46% IBS @ 3 years (depending on severity) and 7–39% @ 6 years following giardiasis	2–12% CF @3 years (depending on severity) and 3–11% @ 6 years following giardiasis	3–14% IBS @ 3 years (depending on severity) and 2–12% @ 6 years following giardiasis