**Appendix C: Study characteristics and significant statistical outcomes**

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| **Study** | **Infection** | **Participants  (N, % female, mean age, setting, country)** | **Follow up %** | **Design and  Statistical method** | **Analysed variables** - prospective - measured in relation to fatigue outcome | **Fatigue outcome - method - measure** | **Fatigue measurement time points** | **Significant statistical outcomes** |
| Candy et al. 2003 | IM (positive IM serology) | N = 71 60% female Mean age = 22.9 (s.d. = 8.2) Three haematology and two virology labs, six general practices and a student healthcare centre. Country: UK | 3 months: 69% 6 months: 87%  12 months: 70% | Prospective cohort   Mann-Whitney U-test Univariate Logistic regression OR | Risk factor variables: activated CD4 and CD8 cytotoxic T cells, cortisol concentration, cortisol concentration change baseline -6 months, more than one recent adverse life event, childhood experience of illness in family, past history of emotional problems, doing regular sport, 10+ days off sick, 'recovered' at interview, given advice to rest by GP, high total symptom, high symptoms severity, low physical functioning, poor physical functioning in last month, poor emotional functioning in last month, poor functioning on Work and Social Adjustment Scale (WSAS), GHQ-12>5 (psychological distress), low control/cure (IPQ), high consequences (IPQ), expect recovery will take >1 month. | Questionnaire Chalder Fatigue Scale | baseline,  3 months,  6 months,  12 months | Fatigue at 3 months was associated with higher acute phase % of activated CD4 (U=5.0, p=.02) and activated CD8 (U=7.0, p=0.039).  All the following are significant at p<.05: Fatigue at 3 months was also associated with high total symptom (OR 8.6, 95% CI 2.0-37), high symptom severity (OR 12, 95% CI 2.8-52), low physical functioning (OR 4.5, 95% CI 1.3-15), poor physical functioning in last month (OR 6.7, 95% CI 1.6-28), poor functioning on WSAS (OR 20, 95% CI 3.8-1.4 [sic]), GHQ-12>5 (OR 11, 95% CI 2.7-42), high consequences (OR 5.8, 95%CI 1.6-20) and expect recovery will take >1 month (OR 8.4, 95% CI 2.0-36). Fatigue at 6 months was associated with GHQ-12>5 (OR 2.8, 95% CI 1.0-8.1), high consequences (OR 3.0, 95% CI 1.0-9.0) and expect recovery will take >1 month (OR 3.4, 95% CI 1.1-11). Fatigue at 12 months was associated with high total symptom (OR 5.7, 95% CI 1.4-24) and poor functioning on WSAS (OR 6.5, 95% CI 1.5-27). |
| Cope et al. 1994 | 'viral illness' (diagnosis) | N = 618 63.5% female Mean age  Male = 29.20 (s.d.= 7.7) Female = 30.15 (s.d.= 7.7) Setting: 42 general practices Country: UK | 81.20% | Prospective cohort  t-test Logistic regression OR | Risk factor variables: GP sick note, GP diagnosis, medication, previral fatigue, symptoms, virus beliefs, GHQ-3 score (psychological distress), attributional style (psychologising, somatising, normalising) | Questionnaire Fatigue Questionnaire  (David et al., 1990) | 6 months | Fatigue at 6 months was associated with receiving a sick note during infection (OR 1.68, 95% CI 1.05-1.54, p=.01), less certain diagnosis of viral illness (X2=19.26, p=.02), GHQ-3 scores at initial presentation (p=.004), higher psychologising attribution scores (p<.05), higher somatising attribution scores (p<.05), lower normalising attribution scores (p<.05), belief that catch virus when rundown or under stress (sub-scale) (t=3.02, p=.003). |
| Cope et al. 1996 | 'viral illness' (diagnosis) | N = 128, Cases N=64, 78% female, mean age = 30.5 (s.d. = 6.5) Controls N = 64, 78% female, mean age = 31.4 (s.d. = 7.3) Setting: General practice Country: UK | 78% | Prospective cohort (case-control)  Logistic regression OR | Risk factor variables: GHQ-3 score (psychiatric morbidity), attributional style, sick certification, presence of fatigue (at time of viral illness), past psychiatric history (verified by GP records). | Interview CFS  (Oxford criteria) | 6 months | CFS at 6 months was associated with sick certification (p=.002, OR 8.5, CI 4.2-17.2), a psychological symptom attributional style (p=.007, OR 2.1, CI 1.6-2.7) and presence of fatigue at time of viral illness (p=.05, OR 6.4, CI 2.5-16.4). |
| Hickie et al. 2006 | EBV, Q fever, RRV (positive serology tests) | N = 253 43% female Mean age = 34 (16-77) Setting: Family practitioner practices, four diagnostic pathology laboratories Country: Australia | 90.5% | Prospective cohort  Stepwise multiple regression - standardised beta co-efficient | Risk factor variables: acute sickness, irritability, musculoskeletal pain, mood disturbance, neurocognitive disturbance, fatigue, premorbid psychiatric disorder, intercurrent psychiatric disorder, neuroticism score, locus of control score | Questionnaire SOMA subscale of SPHERE  Interview CFS  (CDC criteria) | 3 months, 6 months, 12 months | Fatigue at 3 months was associated with irritability (b=0.24, p<.05), musculoskeletal pain (b=0.27, p<.05), neurocognitive disturbance (b=0.24, p<.05) and fatigue (b=0.50, p<.001). CFS at 6 months was associated with musculoskeletal pain (b= 0.30, p<.05) and fatigue at baseline (b= 0.35, p<.001).  CFS at 12 months was associated with fatigue at baseline (b= 0.27, p<.05) |
| Hotopf et al. 1996 | acute onset viral meningitis (clinical diagnosis)  (controls - other viral diagnoses) | N = 159 (83 patients, 76 controls) Cases 64% female Controls 46% female Mean ages: 32 and 31 Setting: Four virology laboratories and specialist hospitals. Country: UK (?) |  | Prospective case-control  Logistic regression OR (adjusted) | Risk factor variables: psychiatric history | Questionnaire Chalder Fatigue Scale CFS  (Oxford criteria, CDC criteria) | 6-24 months post onset (mean = 18 months) | Psychiatric history was a risk factor for CFS (Oxford criteria) (OR 3.58, 95% CI 1.2-10.6, p=.02) and CFS (CDC criteria) (OR 7.82, 95% 1.8-34.3, p=.006), but not chronic fatigue (as measured on the Chalder Fatigue Scale) (OR = 1.33, 95% CI 0.5-3.4, p=.55). |
| Huang et al. 2010 | IM (positive monospot lab records) | N = 301 CFS N=39, 89.7% female Controls N=39 'adolescents' Setting: clinical care sources e.g. school clinics, paediatric practices, virology lab of hospital. Country: USA  Same cohort as Katz et al. (2009) |  | Prospective cohort (case-control)  t-test Compare CFS cases v controls | Risk factor variables:  (measured for 'before' and 'during mono'): Physical Activity: 20-Minute hard exercise, 20-Minute light exercise, Television/video/computer, Sleep, Napping, Other sedentary activity.  Fatigue severity at baseline. | Interview CFS  (CDC criteria - revised by Jason et al. 2006) | 6 months | CFS at 6 months was associated with fatigue severity at baseline, t(39)=3.70, p<.001. |
| Jason et al. 2014 | IM (positive monospot test) | N = 301  CFS: N = 39, 89.7% female, mean age = 16.09 (1.4), 87.2% Caucasian Controls: N = 50, 74% female, mean age = 16.1 (1.5), 94% Caucasian Setting: clinical care sources e.g. school-based health clinics.  Country: USA  Same cohort as Katz et al. (2009) | 53 of 70 'not recovered'=75.7%  39/53 classified as CFS. | Prospective cohort  (case-control)  Logistic regression b, Wald *X*2, OR. | Risk factor variables: autonomic symptoms, perceived stress score, life events score, family stress (around or prior to mono onset?, continuing?, since mono any family stress?, continuing?), days spent in bed, days of school missed, hard time attending school regularly?, difficulties with concentrating, learning or remembering, at least one current psychiatric diagnosis, total number of current diagnoses received. | Interview CFS  (Jason et al. (2006) revision of the CDC criteria) | 6 months | CFS at 6 months was associated with autonomic symptoms (b=.14, *X*2=22.23, OR 1.15, p<.001), perceived stress (b=.10, *X*2=9.81, OR 1.10, p<.001), life events (b=.60, *X*2=13.14, OR 1.83, p<.001), days spent in bed (b=.08, *X*2==5.98, OR 1.08, p=.01), days of school missed (b=.09, *X*2=5.89, OR 1.09, p=.01), at least one current psychiatric diagnosis (b=1.39, *X*2=9.28, OR 4.00, p<.001) and total number of current diagnoses received (b=.68, *X*2=5.13, OR 1.97, p=.02). |
| Katz et al. 2009 | IM (positive monospot test) | N = 301 CFS N=39, 90% female Controls N=50 'adolescents' Setting: clinical care sources e.g. school clinics, pediatric practices, virology lab of hospital. Country: USA | 53 of 70 'not recovered'=75.7%  39/53 classified as CFS. | Prospective cohort  (case-control)  Fisher's exact test *X*2 | Risk factor variable: prescribed steroid treatment during acute episode of mononucleosis. | Interview CFS  (CDC criteria - revised by Jason et al., 2006)  (Questionnaire Chalder Fatigue Scale) | 6 months, 12 months, 24 months | none |
| Kremers et al. 2014 | Q-fever (positive serology) | N = 102 35.3% female Mean age = 48 (s.d. = 16) Setting: Microbiology & Infection Control Hospital Department.  Country: Netherlands | 70.70% | Prospective cohort  Mann Whitney U test | Risk factor variables: interleukin-6 and C-reactive protein levels. | Questionnaire Nijmegen Clinical Screening Instrument: fatigue sub-domain | 4 years after diagnosis | none. |
| Löwe et al. 2014 | Shiga Toxin-Producing Escherichia coli 0104 (STEC)  (clinical diagnosis) | N = 389 69% female Mean age = 46 (s.d. = 17) Setting: 13 hospitals Country: Germany | 79% | Prospective cohort  Multiple linear regression | Risk factor variables: prior psychiatric disorder, prior traumatic event, diarrhoea in the past 4 months, pre-existing chronic condition (e.g. IBS, fibromyalgia), neuroticism, pessimism, optimism, self-efficacy, duration of in-patient treatment (weeks), treatment in intensive care unit, haemolytic uremic syndrome, neurological symptoms, more than 4 instances of diarrhoea on 3 or more days, abdominal pain, length of bloody diarrhoea, fever, fear of death, social support. | Questionnaire Chalder Fatigue Scale (validated German version) (Martin et al., 2010) | 6 months ("fatigue persisting for 3 or more consecutive months"). | Fatigue at 6 months was associated with pre-existing chronic condition (b = 1.75, 95% CI 0.43-3.07, p=.009), neuroticism (b = 1.22, 95% CI 0.20-2.23, p=.019) and treatment in intensive care unit (b = 1.73, 95% CI 0.03-3.43, p=.046). |
| Moss-Morris et al. 2011 | Glandular fever (GF) (positive monospot or serology test) | N = 246 62% female Mean age = 22.8 (s.d. = 8.3) 96% NZ European, 2% Asian, 2% Maori  Setting: community clinical diagnostic service. Country: New Zealand | 91% - 3 months  88% - 6 months | Prospective cohort  (case-control)  Independent sample t-tests and *X*2 tests. Individual logistic regression OR. | Risk factor variables: mean GF symptoms, mean non-GF symptoms, doctor's advice to rest, doctor's advice to avoid exercise, doctor's advice to take medication, perceived stress, negative perfectionism, anxiety, depression, illness identity, timeline, consequences, personal control, illness coherence, emotional representations, all-or-nothing behaviour, limiting behaviour. | Questionnaire CFS  (CDC or Oxford criteria) | 3 months  6 months | Fatigue at 3 months was associated with non-GF somatic symptoms (t(222) = -4.51, p<.001), anxiety (OR 1.22, 95% CI 1.08-1.38, p=.002), depression (OR 1.26, 95% CI 1.09-1.46, p=.002), illness identity (OR 1.17, 95% CI 1.01-1.35, p=.03), timeline (OR 1.3, 95% CI 1.09-1.54, p=.004), consequences (OR 1.15, 95% CI 1.02-1.29, p=.03), personal control (OR 0.86, 95% CI 0.75-0.98, p=.02), illness coherence (OR 0.75, 95% CI 0.62-0.92, p=.01), emotional representations (OR 1.17, 95% CI 1.06-1.29, p=.002), all-or-nothing behaviour (OR 1.13, 95% CI 1.03-1.24, p=.01). CFS at 6 months was associated with non GF somatic symptoms (t(215) = -2.19, p=.03), negative perfectionism (OR 1.08, 95% CI 1.01-1.16, p=.04), anxiety (OR 1.18, 95% CI 1.03-1.34, p =.02), depression (OR 1.26, 95% CI 1.06-1.50, p=.01), timeline (OR 1.38, 95% CI 1.11-1.72, p=.004), illness coherence (OR 0.77, 95% 0.62-0.95, p=.01), emotional representations (OR 1.11, 95% CI 1.00-1.24, p=.05), all-or-nothing behaviour (OR 1.14, 95% CI 1.02-1.26, p=.02). |
| Petersen et al., 2006 | IM (positive antibody test)  (2 comparative cohorts - influenza and tonsillitis) | N=1438 (1318 not including pre-morbid fatigue). Median age = 19 years Setting: General practices (General Practice Research Database). Country: UK | n/a | Prospective cohort  (matched, historic)  Univariate regression OR  Multivariable logistic regression | Risk factor variables: lymphadenopathy within 2 months of positive test, number of GP consultations in year before onset, number of sickness certificates in the year before onset, premorbid anxiety or depressive (mood) disorder, premorbid fatigue, premorbid atopy (eczema, asthma or hay fever). | Database codes: Fatigue symptoms and diagnoses | Fatigue: in year after onset (median = 55 days) | Fatigue after IM was associated with premorbid fatigue (OR 2.0, 95% CI 1.2-3.1, p=.004), 3+ GP consultations in the year before IM (OR 1.7, 95% CI 1.2-2.3, p=.002) and premorbid mood disorder (OR 2.6, 95% CI 1.4-4.8, p=.002). |
| Schur et al. 2007 | IM (positive monospot test) | N = 150 53% female Mean age = 21.3 (s.d. = 6.7) 90% Caucasian Setting: Health maintenance organisation.  Country: USA | 95% | Prospective cohort  Logistic Regression OR (unadjusted and adjusted) | Risk factor variables: BMI at baseline, weight change from baseline to 6 months | Questionnaire 4-item vitality subscale of Medical Outcomes SF-36 health survey | baseline, 6 months | none |
| Seet et al. 2007 | Dengue infection (serologically confirmed) | N = 127  44.1% female Mean age=36.06 (s.d.=13.722) 75.6% Chinese, 17.3% Malay, 4.7% Indian Setting: Hospital Country: Singapore | 100% | Prospective cohort  Multivariate logistic regression OR | Risk factor variables:  Symptoms: fever, nausea, chills, poor appetite, fatigue, cough, abdominal pain, vomiting, diarrhoea, rashes, muscle pain, headaches.  Laboratory parameters: (concentrations of…) White cell count, haemoglobin, haematocrit, platelet, sodium, potassium, urea, creatinine, albumin, total bilirubin, aspartate transaminase, alkaline transaminase, alkaline phosphatase, lactate dehydrogenase. Prothrombin time, activated thromboplastin time. Dengue severity (dengue haemorrhagic fever) | Questionnaire  Chalder Fatigue Scale | 2 months following hospitalisation | Fatigue 2 months after infection was associated with: presence of chills (OR 6.904, 95% CI 1.157-41.202, p=.034) and absence of rashes (OR 0.113 95% CI 0.017-0.774, p=.026). |
| van Loenhout et al. 2015 | Q-fever 'lab confirmed' | N = 336 48.5 % female Mean age = 48.5 (s.d. = 13.9) 98.5 % Dutch Setting: Municipal Health Services Country: Netherlands | 82.74% | Prospective cohort  Multivariate regression | Risk factor variables: pre-existing health problems, diagnosis during the acute Q-fever episode. | Questionnaire Nijmegen Clinical Screening Instrument: fatigue sub-domain | 12 and 24 months | Pre-existing health problems were associated with fatigue at 12 months, b = 4.45, CI 0.79 - 8.10, p=.017, and 24 months, b = 7.41, CI 3.65 - 11.17, p<.001. |
| Wessley et al. 1995 | General infections | N=1167 of 1199 exposed, 68% female, mean age = 32.7 (s.d.=7.5)  N=671 from exposed cohort with complete data from all stages.  Setting: Community sampling. General practices Country: UK | 84% | Prospective cohort  (cohort and case-control)  *X*2  Independent regression OR | Risk factor variables: pre-onset fatigue, pre-onset psychological distress, psychological distress at time of infection, belief that fatigue at presentation was due to a physical cause, viral symptoms, local symptoms. | Questionnaire  Fatigue Scale  (Chalder) | Community screening, baseline, 6 months | Fatigue at 6 months was associated with premorbid fatigue (OR 3.0, 95% 1.9-4.7, p<.001), pre-onset psychological morbidity (OR 1.8, 95% CI 1.2-2.9, p=.009), psychological morbidity at time of infection (OR 1.8, 95 CI, p=.01) and higher number of general viral symptoms (no data). |
| White et al. 2001 | IM (positive monospot and 10%+ atypical lymphocytes) and non-IM (other diagnosed infections)  (upper respiratory tract infection comparison group) | N = 250 (118 IM, 127 non-IM, 5 excluded) 51% female Setting: City University, London. St Bartholomew's Hospital, London General surgeries Country: UK |  | Prospective cohort  Stepwise logistic regression;  Univariate Relative Risk | Risk factor variables: cervical lymphadenopathy, atopy, AST at 1 month, yGT at 1 month, bilirubin at 1 month, fatigue at onset, time in bed at onset, exercise power, fitness, GP attendance in year before onset, premorbid psychiatric disorder (PPD) at any time, PPD in year before onset, PPD in 2 weeks before onset, GP record of PPD, GP record of any PPD treatment, premorbid mood disorder (PMD) at any time, PMD in year before onset, PMD in 2 weeks before onset, GP record of PMD, depression at 1 month, anxiety at 1 month, self-rated extroversion, relative rated extroversion, self-rated emotionality, relative-rated emotionality | Interview Empirically defined fatigue syndrome (White et al., 1995). CFS:  Oxford criteria CDC criteria | 1, 2, 6 months after symptom onset. Primary care records examined 2.5 years later. | Fatigue at 2 months was associated with cervical lymphadenopathy (RR 4.9, CI 2.5-9.7), AST at 1 month (RR 2.4, 95% CI 1.3-4.5), fatigue at onset (RR 2.0, 95% CI 1.3-3.0), time in bed at onset (RR 2.0, 95% CI 1.2-3.2), lower fitness (RR 0.6, 95% CI 0.4-1.0). Fatigue at 6 months was associated with AST at 1 month (RR 2.3, 95% CI 1.0-4.8), fatigue at onset (RR 2.1, 95% CI 1.0-4.3), lower fitness (RR 0.4, 95% CI 0.2-0.9), GP record of PMD (RR 2.1, 95% CI 1.0-4.4), depression score (RR 2.1, 95% CI 1.0-4.5). CFS (Oxford criteria) at 6 months was associated with time in bed at onset (RR 3.2, 95% CI 1.5-7.1), lower fitness (RR 0.4, 95% CI 0.2-0.9), GP attendance in year before onset (RR 4.1, 95% CI 1.7-10.3), GP record of PPD (RR 4.0, 95% CI 2.2-7.4), GP record of any PPD treatment (RR 3.7, 95% CI 2.0-6.8), PMD at any time (RR 2.1, 95% CI 1.2-3.8), PMD in 2 weeks before onset (RR 2.9, 95% CI 1.5-5.6), GP record of PMD (RR 3.5, 95% CI 2.0-6.3), anxiety score (RR 3.9, 95% CI 1.4-11.0), mood disorder at 2 months (RR 4.4, 95% CI 2.6-7.5), self-rated emotionality (RR 1.9, 95% CI 1.0-3.5, p<.05), relative-rated emotionality (RR 2.3, 95% CI 1.2-4.2). CFS (CDC criteria) at 6 months was associated with time in bed at onset (RR 2.2, 95% CI 1.1-4.6), lower fitness (RR 0.5, 95% CI 0.2-1.0), GP attendance in year before (RR 3.0, 95% CI 1.3-7.0), GP record of PPD (RR 2.3, 95% CI 1.2-4.6), PMD at any time (RR 2.2, 95% CI 1.2-3.9), PMD in 2 weeks before onset (RR 2.8, 95% CI 1.4-5.8).  p<.05 for all. |